Patterson's
Allergic Diseases

EIGHTH EDITION

Leslie C. Grammer

Paul A. Greenberger

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Leslie C. Grammer, MD

Director
Ernest S. Bazley Asthma and Allergic Diseases Center

Professor
Northwestern University Feinberg School of Medicine

Clinic Practice Director
Division of Allergy-Immunology
Northwestern University
Chicago, Illinois

With

Paul A. Greenberger, MD

Professor
Feinberg School of Medicine

Associate Chief
Education and Clinical Affairs
Division of Allergy-Immunology
Northwestern University Feinberg School of Medicine

Attending Physician
Northwestern Memorial Hospital
Chicago, Illinois

LWW.com

Preface

Our goal is for the 8th edition of *Patterson's Allergic Diseases* to be an excellent source of current practical information just as the first edition was when it was published in 1972 with Dr Roy Patterson as the sole editor. He was an extremely gifted clinical allergist-immunologist, investigator, and educator, a true "triple threat." We are committed to extending Roy's tradition of allergy-immunology excellence with this newest edition, which we believe is replete with knowledge that continues to exponentially expand in our fascinating field. We have es-pecially tried to include references to the most recent evidence-based guidelines including the Practice Parameters from The Joint Task Force (JTF) on Practice Parameters, which was formed in 1989, and comprises members from the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma, and Immunology.

Like every edition before it, this book is written principally as a guide for physicians and other health care providers. Although it is intended to be oriented toward patient evaluation and management, there are also discussions of underlying immunologic mechanisms, pathophysiology, pharmacology, and diagnostic techniques. Because atopic diseases are common and becoming increasingly prevalent, we hope that a variety of health care providers will find this edition useful as they care for patients with allergic and other immunologic diseases. We have added two new chapters dealing with laboratory tests in allergy-immunology and personalized medicine in the discipline of allergy-immunology.

We believe that caring for patients with atopic diseases sometimes is best accomplished in collaboration with physicians from other specialties. Therefore, about one quarter of the chapters are written by other specialists with whom the allergist-immunologist is likely to collaborate. Those specialties include dermatology, gastroenterology, otolaryngology, psychiatry, pulmonology, and radiology. We are indebted to each of the contributing authors and hereby express our heartfelt gratitude for their participation in this 8th edition of

Patterson's Allergic Diseases.

Leslie C. Grammer, MD

Paul A. Greenberger, MD

Contributing Authors

Sultan Alandijani, MD

Instructor

Department of Internal Medicine

Division of Allergy and Immunology

University of South Florida

Tampa, Florida

Andrea J. Apter, MD, MA, MSc

Professor

Department of Medicine

Section of Allergy & Immunology

Division of Pulmonary, Allergy, & Critical Care

University of Pennsylvania School of Medicine

Philadelphia, Pennsylvania

Pedro C. Avila, MD

Allergist-Immunologist

Allergy and ENT Associates

Woodlands, Texas

Melvin Berger, MD, PhD

Adjunct Professor

Pediatrics and Pathology

Case Western Reserve University

Cleveland, Ohio

Senior Director

Medical Research and Education

Global Medical Affairs

CSL Behring, LLC

King of Prussia, Pennsylvania

David I. Bernstein, MD

Professor of Clinical Medicine & Environmental Health

Department of Internal Medicine

Division of Immunology

University of Cincinnati Medical Center

Cincinnati, Ohio

Jonathan A. Bernstein, MD

Professor

Department of Internal Medicine

Division of Immunology/Allergy

University of Cincinnati College of Medicine

Cincinnati, Ohio

Gregory D. Brooks, MD

Associate Professor

Department of Medicine

Section of Allergy, Pulmonary and Critical Care

University of Wisconsin School of Medicine and Public Health

Madison, Wisconsin

Wesley Burks, MD

Professor

University of North Carolina at Chapel Hill

Chapel Hill, North Carolina

Robert K. Bush, MD

Professor

Department of Medicine

Section of Allergy, Pulmonary and Critical Care

University of Wisconsin School of Medicine and Public Health

Madison, Wisconsin

Tara F. Carr, MD, FAAAAI

Assistant Professor

Division of Pulmonary, Allergy, Critical Care and Sleep Medicine

University of Arizona

Tucson, Arizona

Rakesh Chandra, MD

Associate Professor

Vanderbilt University

Nashville, Tennessee

Seong H. Cho, MD

Associate Professor

Department of Internal Medicine

Division of Allergy and Immunology

University of South Florida

Tampa, Florida

David B. Conley, MD

Professor

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Susan J. Corbridge, PhD, APN, ACND

Clinical Associate Professor

College of Nursing and Department of Medicine

Director of Graduate Clinical Studies

College of Nursing

University of Illinois at Chicago

Chicago, Illinois

Thomas Corbridge, MD, FCCP

Professor

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Jane E. Demattee, MD

Professor of Medicine

Division of Pulmonary and Critical Care Medicine

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Anne M. Ditto, MD

Associate Professor

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Tolly G. Epstein, MD

Assistant Professor

University of Cincinnati Medical Center

Cincinnati, Ohio

Olajumoke O. Fadugba, MD

Assistant Professor

Division of Pulmonary, Allergy, & Critical Care Medicine

University of Pennsylvania School of Medicine

Philadelphia, Pennsylvania

Theodore M. Freeman, MD, FACP, FAAAAI, FACAAI

Allergist-Immunologist

San Antonio Asthma and Allergy Clinic

San Antonio, Texas

Jackie K. Gollan, PhD

Associate Professor

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Nirmala Gonsalves, MD

Associate Professor of Medicine

Division of Gastroenterology & Hepatology

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Leslie C. Grammer, MD

Director

Ernest S. Bazley Asthma and Allergic Diseases Center

Professor

Northwestern University Feinberg School of Medicine

Clinic Practice Director

Division of Allergy-Immunology

Northwestern University

Chicago, Illinois

Thomas Grant, DO, FACR

Professor of Radiology

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Paul A. Greenberger, MD

Professor

Feinberg School of Medicine

Associate Chief

Education and Clinical Affairs

Division of Allergy-Immunology

Northwestern University Feinberg School of Medicine

Attending Physician

Northwestern Memorial Hospital

Chicago, Illinois

Kathleen E. Harris, BS

Research Lab Manager

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Ikuo Hirano, MD

Professor

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Mary B. Hogan, MD

Professor

University of Nevada

Las Vegas, Nevada

Karen S. Hsu Blatman, MD

Instructor

Brigham and Women's Hospital

Harvard Medical School

Boston, Massachusetts

Kathryn E. Hulse, PhD

Research Assistant Professor

Division of Allergy-Immunology

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Ravi Kalhan, MD, MS

Associate Professor of Medicine and Preventive Medicine

Division of Pulmonary and Critical Care Medicine

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Achilles G. Karagianis, DO

Assistant Professor of Neuroradiology

Northwestern University Feinberg School of Medicine

Chief

Head and Neck Radiology

Northwestern Memorial Hospital

Chicago, Illinois

Robert C. Kern, MD

Professor and Chairman

Department of Otolaryngology

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Alexander S. Kim, MD

Assistant Professor

Department of Medicine

University of California San Diego

La Jolla, California

Edwin Kim, MD, MS

Assistant Professor

University of North Carolina at Chapel Hill

Chapel Hill, North Carolina

Jennifer S. Kim, MD

Clinician Educator

Allergy & Immunology

NorthShore University HealthSystem

Senior Clinician Educator

Pritzker School of Medicine

University of Chicago

Chicago, Illinois

Barry Ladizinski, MD

Instructor

Division of Dermatology

John H. Stroger, Jr. Hospital of Cook County

Chicago, Illinois

Theodore M. Lee, MD

Clinical Faculty

Department of Medicine

Division of Pulmonary, Allergy & Critical Care

Emory University School of Medicine

Peachtree Allergy and Asthma Clinic, PC

Atlanta, Georgia

Tabi Leslie, MD

Consultant Dermatologist

Department of Dermatology

Royal Free Hospital

London, United Kingdom

Donald Y. M. Leung, MD, PhD

Professor

Head, Division of Pediatric Allergy & Immunology

Department of Pediatrics

National Jewish Health

University of Colorado–Denver

Denver, Colorado

Estelle Levetin, PhD

Professor

Faculty of Biological Science

University of Tulsa

Tulsa, Oklahoma

Phil Lieberman, MD

Clinical Professor

Departments of Medicine and Pediatrics

Division of Allergy and Immunology

University of Tennessee

Memphis, Tennessee

Umbreen S. Lodi, MD

Assistant Professor

Department of Medicine

Division of Pulmonology, Allergy & Critical Care

Emory University School of Medicine

Department of Allergy/Immunology

Emory University/Grady Hospital

Atlanta, Georgia

Mahboobeh Mahdavinia, MD, PhD

Assistant Professor

Department of Internal Medicine

Division of Allergy and Immunology

Rush University Medical Center

Chicago, Illinois

Melanie M. Makhija, MD

Assistant Professor

Northwestern University Feinberg School of Medicine

Ann and Robert H. Lurie Children's Hospital of Chicago

Chicago, Illinois

Erin N. McComb, MD

Assistant Professor

Department of Radiology

Northwestern Memorial Healthcare

Chicago, Illinois

Kris G. McGrath, MD

Professor of Medicine

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Sheniz Moonie, MD

Associate Professor

School of Community Health Sciences

Epidemiology and Biostatistics Program

University of Nevada, Las Vegas

Las Vegas, Nevada

Michelle J. Naidich, MD

Assistant Professor

Department of Radiology

Northwestern Memorial Healthcare

Chicago, Illinois

Peck Y. Ong, MD

Associate Professor of Clinical Pediatrics

Department of Pediatrics

Division of Clinical Immunology and Allergy

University of Southern California Keck School of Medicine

Children's Hospital Los Angeles

Los Angeles, California

Snehal Patel, DO

Fellow

Division of Pulmonary, Allergy, Critical Care and Sleep Medicine

University of Arizona

Tucson, Arizona

Anju T. Peters, MD

Professor

Department of Medicine

Division of Allergy-Immunology

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Neill T. Peters, MD

Clinical Instructor

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Jacqueline A. Pongracic, MD

Professor

Departments of Pediatrics and Medicine

Division of Allergy-Immunology

Northwestern University Feinberg School of Medicine

Ann and Robert H. Lurie Children's Hospital of Chicago

Northwestern Memorial Hospital

Chicago, Illinois

David C. Reid, MD

Dermatologist

Division of Dermatology

John H. Stroger, Jr. Hospital of Cook County

Chicago, Illinois

Anthony J. Ricketti, MD

Clinical Assistant Professor

Department of Medicine

Rowan University School of Osteopathic Medicine

Stratford

Mercer Allergy and Pulmonary Associates, LLC

Trenton, New Jersey

Peter A. Ricketti, MD

Fellow

Department of Internal Medicine

Division of Allergy and Immunology

Morsani College of Medicine

University of South Florida

Tampa, Florida

Rachel G. Robison, MD

Assistant Professor of Pediatrics

Department of Pediatrics

Division of Allergy-Immunology

Northwestern University Feinberg School of Medicine

Attending Physician

Ann & Robert H. Lurie Children's Hospital of Chicago

Chicago, Illinois

Karolina Roszko, MD

Dermatologist

University of Illinois at Urbana-Champaign

Champaign, Illinois

Eric J. Russell, MD, FARC

Chairman

Department of Radiology

Northwestern University Feinberg School of Medicine

Attending Physician

Department of Radiology

Northwestern Memorial Healthcare

Chicago, Illinois

Carol A. Saltoun, MD

Assistant Professor

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Hatice Savas, MD

Assistant Professor

Department of Radiology

Division of Thoracic Imaging

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Andrew J. Scheman, MD

Associate Professor of Clinical Dermatology

Department of Dermatology

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Rahul Sharma, MD

Fellow

Department of Medicine

Division of Pulmonary and Critical Care Medicine

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Whitney W. Stevens, MD, PhD

Assistant Professor

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Rachel E. Story, MD

Clinician Educator

Pritzker School of Medicine

University of Chicago

Attending Physician

NorthShore University HealthSystems

Glenview, Illinois

Sherlyana Surja, MD

Instructor

Department of Internal Medicine

Section of Allergy & Immunology

Division of Allergy and Immunology

Rush University Medical Center

Chicago, Illinois

Abba I. Terr, MD

Professor Emeritus

Department of Medicine

University of California San Francisco School of Medicine

San Francisco, California

Ravi K. Viswanathan, MD

Assistant Professor (CHS)

Department of Medicine

Section of Allergy, Pulmonary and Critical Care

University of Wisconsin School of Medicine and Public Health

Madison, Wisconsin

Stephen I. Wasserman, MD

Professor of Medicine

School of Medicine

University of California San Diego

La Jolla, California

Carol A. Wiggins, MD

Clinical Assistant Professor

Department of Medicine

Emory University School of Medicine

Piedmont Hospital

Atlanta, Georgia

Nevin W. Wilson, MD

Professor and Chair of Pediatrics

Department of Pediatrics

University of Nevada Las Vegas School of Medicine

Las Vegas, Nevada

Lisa Wolfe, MD

Associate Professor

Department of Medicine

Division of Pulmonary and Critical Care Medicine

Northwestern University Feinberg School of Medicine

Chicago, Illinois

Chester R. Zeiss, MD

Professor Emeritus

Northwestern University Feinberg School of Medicine

Jesse Brown VA Medical Center

Chicago, Illinois

Michael S. Ziffra, MD

Assistant Professor

Department of Psychiatry and Behavioral Sciences

Northwestern University Feinberg School of Medicine

Chicago, Illinois

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In particular, we owe a debt of gratitude to all of the following for their support in producing this book:

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CHAPTER 1

Review of Immunology

KATHRYN E. HULSE

■ INTRODUCTION

Although immunology is a relative newcomer among the sciences, its phenomena have long been recognized and manipulated. Ancient peoples understood that survivors of particular diseases were protected from those diseases for the remainder of their lives, and the ancient Chinese and Egyptians even practiced forms of immunization. Surgeons have also long understood that tissues and organs would not survive when exchanged between different individuals (e.g., from cadaver donors) but could succeed when transplanted from one site to another within the same individual. However, only during the past century have the mechanisms of the immune system been illuminated, at least in part. Our immune system is divided into a fast-acting innate immune response and a slower-responding acquired, or adaptive, immune system, which is present only in vertebrates. The critical cells and effectors of our immune response develop principally in the bone marrow and thymus, although during fetal development, the liver is also an important site of immune cell development. The immune system is honed to respond to and clear an astonishing number of different potentially pathogenic organisms, but it can also be the source of disease when it is not regulated properly. This chapter provides

a basic overview of the major components of the innate and adaptive immune responses in humans, which will be important for understanding many of the concepts presented throughout the remainder of this textbook.

INNATE IMMUNITY

The innate immune system is our first line of defense against potentially pathogenic organisms (1,2). The cells of the innate immune system recognize pathogens through the expression of receptors that are "hard-wired" into our genomes as a result of evolution and selection over the long period of divergence between the microbial world and our own. As a result, the innate immune system is poised to rapidly respond to pathogens and initiate the adaptive immune responses that are generally necessary to fully eliminate pathogens. The innate immune system comprises a wide variety of cells and mediators, which have a multitude of functions, including inhibition of pathogen replication, phagocytosis of infected cells and pathogens, and activation of the adaptive immune response.

Cytokines and Chemokines

Cytokines and chemokines are critical meditators produced by both innate and adaptive immune cells. The term cytokine refers to a large number of different mediators that play a role in immune responses. Cytokines are also often referred to as interleukins (ILs), and they can act in an autocrine (on the same cell that released the cytokine) or paracrine (on a different cell) manner (1,2). Cytokines, and their receptors, are grouped into families based on structural similarities. The four families are the IL-1 family, the hematopoietic family, the interferons, and the tumor necrosis factor (TNF) family (3–5). Cytokines are secreted by cells of the immune system and bind to receptors on other immune cells, or even structural cells, to mediate their effects. Chemokines are another group of small molecules that play a critical role in immunity. Chemokines have conserved cysteine motifs that are critical to their structure, and they are divided into different families based on the specific location of these conserved cysteine motifs (6). All chemokines bind to seven transmembrane G-protein-coupled receptors to mediate their effects. Unlike cytokines, which generally cause activation of their target cells, chemokines induce target cells to migrate in the direction of the chemokine gradient. This effect is critical for the correct movement and positioning of cells at all phases of immune responses.

Pattern Recognition Receptors

The hard-wired receptors of the innate immune system are called pattern

recognition receptors (PRRs) because they recognize evolutionarily conserved microbial patterns (i.e., viral RNA, bacterial lipopolysaccharide [LPS], or flagellin), or they recognize stress signals from infected and/or damaged cells. The microbial patterns recognized by PRRs are also called pathogen-associated molecular patterns (PAMPs), whereas the stress signals are referred to as danger-associated molecular patterns (DAMPs). Cells of the adaptive immune system also express PRRs and can respond to PAMPs, but the innate immune system relies exclusively on PRRs for pathogen recognition. There are four main categories of PRRs in humans.

The toll-like receptors (TLRs) are an evolutionarily conserved family of PRRs that are the mammalian homologue to the Toll protein in Drosophila (7). Ten TLRs have been identified in humans, TLR1–10 (Table 1.1), whereas mice lack TLR10 but express three additional TLRs: TLR11–13 (1). TLRs are expressed as membrane-bound or intracellular receptors, and they can respond to both microbial PAMPs and host cell stress signals. The membrane-bound TLRs recognize PAMPs in the extracellular environment, such as LPS, whereas the intracellular TLRs detect a wide variety of nucleic acids associated with pathogens, such as double-stranded viral RNA. Activation of TLRs leads to the expression of various proinflammatory and antiviral proteins that help to orchestrate the appropriate downstream immune responses necessary to clear the pathogen.

TABLE 1.1 HUMAN TOLL-LIKE RECEPTORS

TLR	CELLULAR LOCATION	LIGAND(S)
TLR1:TLR2 heterodimer TLR2:TLR6 heterodimer	Cell surface	Lipomannans (mycobacteria) Lipoproteins (bacteria) Lipoteichoic acids (bacteria) β-Glucans (bacteria and fungi) Zymosan (fungi)
TLR3	Intracellular	dsRNA (viruses)
TLR4	Cell surface	LPS (bacteria) Lipoteichoic acids (bacteria)

TLR5	Cell surface	Flagellin (bacteria)
TLR7	Intracellular	ssRNA (viruses)
TLR8	Intracellular	ssRNA (viruses)
TLR9	Intracellular	CpG DNA (bacteria)
TLR10	Cell surface	Unknown

dsRNA, double-stranded RNA; LPS, lipopolysaccharide; ssRNA, single-stranded RNA; TLR, Toll-like receptor.

The NOD-like receptors (NLRs) are a conserved family of PRRs with more than 20 different members (8). The NLRs are exclusively expressed in the cytosol, where they recognize a variety of PAMPs and DAMPs, similar to the intracellular TLRs. A key feature of the NLRs is their ability to bind to one another and form oligomers. These NLR oligomers can also recruit additional, unrelated proteins to form signaling complexes. The NLRs can also cooperate with TLRs to induce an inflammatory response. One key response that is mediated by NLRs is the formation of the inflammasome, which plays a critical role in the production of activated IL-1β and IL-18, which are important for the induction of inflammation.

The RIG-I–like receptors (RLRs) are a family of intracellular PRRs that specialize in the recognition of viral RNA (9). There are three members in the RLR family: RIG-I, MDA5, and LGP2. These receptors bind to both single-stranded and double-stranded viral RNA products, which are produced during viral infections. Upon their activation, the RLRs can then trigger expression of important antiviral genes leading to the production of type I interferons. Similar to the NLRs, RIG-I and MDA5 can recruit other signaling molecules to induce an inflammatory response. However, LGP2 cannot itself initiate an inflammatory response, but it does seem to be necessary for the other two RLR members to function effectively (10).

The C-type lectin receptors (CLRs) are a conserved family of PRRs that recognize carbohydrates on the surface of microbes (11). These receptors can be

membrane bound or soluble proteins found in blood and other fluids. Recognition of microbial carbohydrates by CLRs results in the induction of phagocytosis of the microbe and inflammatory responses that activate an adaptive immune response. The CLRs are able to recognize a wide variety of microbial-associated carbohydrates, including mannose, glucose, *N*-acetylglucosamine, and *b*-glucans. This allows the CLRs to respond to a wide variety of potential pathogens, including bacteria, fungi, viruses, and helminths.

Epithelial Cells as Innate Immune Cells

Epithelial cells are not traditionally thought of as immune cells, but they provide our first lines of defense against pathogens through multiple mechanisms (12). First, because epithelial cells form tight junctions between adjacent cells, they are able to form a physical barrier that prevents the entry of foreign microbes and antigens into our tissues. In addition to the formation of tight junctions, many epithelial cells, such as those in the airways and intestines, have cilia and produce mucus. The mucus layer covering many epithelial barriers helps to trap potential pathogens before they can reach the epithelial cells themselves, and the cilia function to sweep cells and debris out of our bodies. These structural defenses play a critical role in preventing exposure to many potential pathogens.

Epithelial cells also have the ability to function as innate immune cells that can trigger a variety of immune responses. They express TLRs, which allows them to respond directly to invading microbes and alert the immune system, and they can express powerful antimicrobial molecules that can directly kill or weaken microbes. Upon recognition of a potential pathogen, epithelial cells are also able to produce proinflammatory chemokines and cytokines. These molecules then function to recruit and activate effector cells of both the innate and adaptive immune systems, including dendritic cells (DCs), innate lymphoid cells (ILCs), granulocytes, and lymphocytes. As such, epithelial cells often play a critical role in orchestrating the induction of immune responses and are a vital part of our innate immune defenses.

Innate Lymphoid Cells

ILCs are a newly defined group of cells that play an important role in innate immunity (13). ILCs develop in the bone marrow from a common lymphoid progenitor (CLP) cell, which also gives rise to T and B lymphocytes (see later) (1). ILCs and T cells share many common functions, but ILCs do not express the T cell receptor (TCR) and thus do not respond to microbes in the same way as T cells. ILCs are important for early recognition of pathogens and cellular damage,

often receiving activating signals from the epithelium, and they function to influence the ensuing adaptive immune response. ILCs can be divided into three main groups based on their function, similar to CD4$^+$ T-helper (Th) cell subsets (see later). The most well-studied ILCs are natural killer (NK) cells, which are part of the ILC1 family. ILC1s depend on the transcription factor T-bet for their development, are activated by IL-12 and IL-18, secrete IFN-γ, and play an important role in defense against viral infections. ILC2s are dependent on the transcription factor GATA-3, are activated by IL-25, IL-33, and TSLP, secrete IL-5 and IL-13, and play an important role in defense against helminthic infections. ILC3s are dependent on the transcription factor RORγt for their development, are activated by IL-1 and IL-23, secrete IL-17 and IL-22, and play an important role in intestinal barrier function and the generation of lymphoid organs.

Myeloid Cells

Myeloid cells are a large family of innate immune effector cells that develop in the bone marrow from the common myeloid progenitor (CMP) cell (1). In addition to expressing a variety of PRRs, many myeloid cells also express Fc receptors. These receptors recognize the Fc portion of antibody molecules, and they play an important role in the activation of myeloid cells during immune responses.

Monocytes are found in the circulation and are capable of phagocytizing microbes and presenting antigens to T cells, but they are not efficient at either of these functions. However, when monocytes enter the tissue in response to an infection, they can rapidly differentiate into macrophages. Macrophages are highly efficient phagocytes that help to destroy invading microbes and present antigens to and activate effector memory T cells. Although macrophages are capable of activating memory T cells, which have a lower threshold of activation, they are not effective activators of naïve T cells. Monocytes can also differentiate into inflammatory DCs in the tissue. In addition, DCs can be derived directly from the CMP in the bone marrow and migrate into tissues themselves. DCs can develop into either conventional DCs, which play a role in a wide variety of immune responses, or plasmacytoid DCs (pDCs), which are critical for induction of immune responses against viruses (1). Conventional DCs serve as immune sentinels in the tissue. Upon microbial infection, they capture antigens via phagocytosis, which activates the DC and triggers its migration to the draining lymph node. Within the lymph node, activated DCs are excellent antigen presenting cells (APCs) and express all the necessary costimulatory

molecules and cytokines needed to efficiently activate naïve T cells.

Granulocytes are another group of myeloid cells that contain different preformed granules in their cytoplasm. These preformed granules contain a variety of molecules that can be rapidly released upon cellular activation, and they function to neutralize pathogens and recruit other immune cells to the site of infection. Neutrophils are the most abundant type of granulocyte in the peripheral blood. During infections, particularly bacterial infections, neutrophils are one of the first innate immune cells to traffic into the infected tissue. Once in the tissue, neutrophils can release their granules through a process called degranulation. These granules contain enzymes (i.e., myeloperoxidase and elastase), and antimicrobial peptides (i.e., defensins) that can kill invading organisms in the tissue. In addition, neutrophils can phagocytose pathogens, which leads to intracellular killing of the microbe. Finally, neutrophils can form a structure called a neutrophil extracellular trap, which is composed of DNAs, enzymes, and antimicrobial peptides that can trap and kill microbes (14).

Eosinophils are another type of granulocyte that compose about 1% to 6% of cells in the peripheral blood. Like neutrophils, eosinophils are also induced to traffic into infected tissues, but eosinophils are more associated with infections by parasites and helminths, as opposed to bacteria. Eosinophils also undergo degranulation in response to infections. Eosinophil granules are composed of toxic molecules that function to kill invading microbes, and they include eosinophil cationic protein and major basic protein. These mediators can form pores in target cell membranes, cause toxic oxidative stress in target cells, activate other immune cells, and increase mucus production.

Basophils are the least common granulocyte in the peripheral blood. Once in the tissue, basophils can degranulate and release a variety of inflammatory mediators that function to kill pathogens. These mediators include histamine and proteoglycans. After their initial activation and degranulation, usually in response to IgE (see later), basophils can also release cytokines, such as IL-4, and proteolytic enzymes, including elastase. These molecules function to activate other immune cells, particularly T cells, and help in the destruction of the pathogen. Mast cells are granulocytes that are similar to basophils. However, unlike the other granulocytes, mast cells do not fully mature until they reach the tissues and thus are not found in the circulation. Mast cells are also activated by IgE to undergo degranulation. Mast cell granules contain, among other mediators, histamine and *b*-hexsoaminidase, and they can also produce prostaglandins, IL-4, and TNF after activation. Along with eosinophils and

basophils, mast cells play a critical role in the response to parasite infections, but they are also associated with allergic disease and anaphylaxis.

ADAPTIVE IMMUNITY

The adaptive immune response is often our last line of immune defense. Unlike the innate immune response, the effector cells of the adaptive response are able to recognize a multitude of highly specific antigenic structures, and they provide long-lasting protection against encountered antigens through the formation of a memory response (1,2). The adaptive response also takes more time to develop than the innate response. The main effector cells of the adaptive immune system are the T and B lymphocytes.

Antigens

Antigens are any substance that can bind to the specific lymphocyte receptors, that is, the TCR and the B cell receptor (BCR). Antigens can be derived from foreign substances, such as an invading virus or bacteria, or from our own cells, and they may or may not induce an immune response. Antigens that specifically trigger an adaptive immune response are called immunogens, and the terms antigen and immunogen are often used interchangeably. In contrast, a tolerogen is a substance that after an initial exposure to the immune system inhibits future responses against itself. Because of the genetic diversity among individuals, a substance that is an immunogen for one person may be a tolerogen for another and may go unrecognized by the immune system of yet another. Also, a substance that acts as an immunogen when administered by one route (e.g., intramuscularly) may act as a tolerogen when applied by a different route (e.g., orally), in a different form (e.g., denatured), or following treatment of the individual with therapeutic agents.

In addition to antigens, there are other molecules that contribute to activation of adaptive immune responses through the TCR and/or BCR. A hapten is a small molecule that cannot stimulate an immune response on its own. However, if a hapten is attached to a larger immunogenic molecule (a "carrier"), immune responses can be stimulated against both the carrier and the hapten, and the hapten itself can subsequently serve as the target of a response. Similarly, adjuvants are substances that enhance the immune response to an immunogen. Unlike a hapten, adjuvants are not directly linked to the immunogen but are delivered at the same time. Adjuvants are often used in vaccines to ensure that a robust adaptive immune response is generated.

T Cell Antigen Recognition

T lymphocytes, or T cells, initially develop from the CLP in the bone marrow but then travel to the thymus for the majority of their differentiation (1). Within the specialized microenvironment of the thymus, developing T cells transition through a series of distinct developmental stages that lead to the generation of mature naïve T cells. A key step in this process is the expression of a unique antigen recognition receptor, the TCR, on each T cell clone. The TCR recognizes antigens, mainly peptides, that are presented in the context of major histocompatibility complex (MHC) molecules expressed on other cells. The TCR is a heterodimer composed of either an α and β or a γ and δ chain, and it forms a complex with CD3, which is expressed on, and unique to, all T cells. In addition, the TCR usually pairs with a co-receptor, either CD4 or CD8, which is expressed on specific subsets of T cells. During development in the thymus, all T cells undergo a brief stage where they express both CD4 and CD8, but in the periphery, αβ T cells express only one of these two receptors, whereas γδ T cells often do not express either.

TCRs are generated via a unique process that has the capacity to generate up to 10^{18} different receptors with unique specificities. Each individual T cell expresses only one unique TCR, and the ability to generate such a wide variety of unique TCRs is critical for the immune system's ability to recognize and respond to antigens from a wide variety of pathogens and confer protection. Each of the two chains of the TCR is composed of a variable and constant region (Fig. 1.1). The variable region determines which peptide/MHC complex the TCR will bind to, and thus it confers antigen specificity. Unlike most other proteins, the chains of the TCR are not encoded by a single gene. Instead, they are encoded by a series of genes that occur in clusters, which are randomly recombined during thymic T cell development through a process termed V(D)J recombination (Fig. 1.1). During this process, random V, D (in the case of the β and δ chains), and J gene segments are selected and recombined to form a unique variable region. The α chain is composed of one V gene segment and one J gene segment, whereas the β chain is composed of one V gene segment, one D gene segment, and one J gene segment. Additional variability is introduced by the imprecise cutting and annealing of each gene segment and the random addition of nucleotides to fill in these gaps, which is termed junctional diversity. All the intervening genomic DNA between the selected gene segments is removed during this process. Once a T cell has successfully undergone V(D)J recombination, all its progeny will express the same TCR clone and have the

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same antigen specificity.
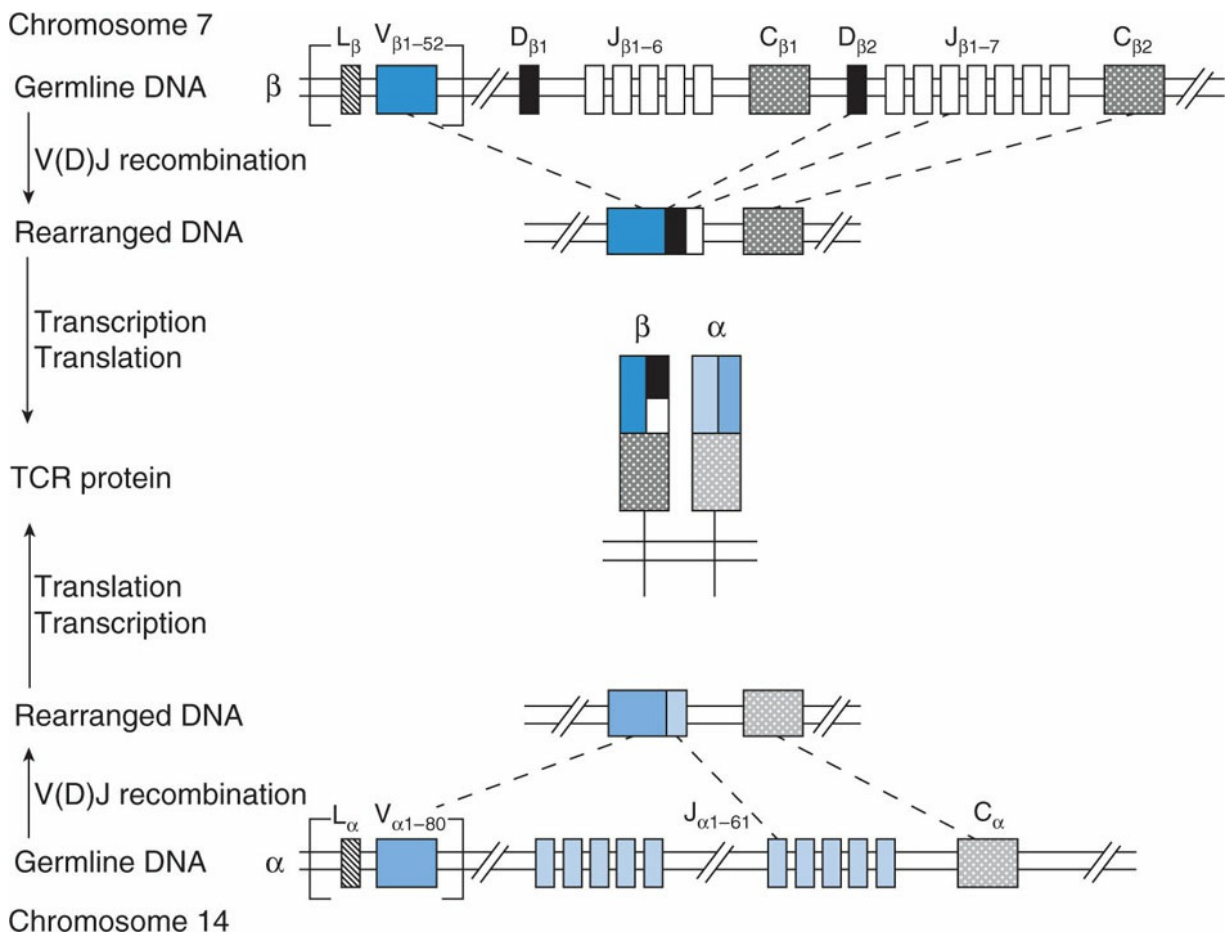
■ FIGURE 1.1 Generation of the T cell receptor (TCR).

In general, TCRs recognize only antigenic peptides presented by MHC molecules (Fig. 1.2). In humans, the MHC molecules are encoded by the genes of the human leukocyte antigen (HLA) region. The MHC locus contains more than 200 MHC class I and class II genes, and it is highly polymorphic. As such, each person will generally express at least three different MHC class I molecules and three or four different MHC class II molecules. This diversity of MHC molecules ensures that a wide variety of antigenic peptides will be able to be presented to T cells. The class I MHC molecules are encoded by the HLA-A, -B, and -C loci, whereas the class II MHC molecules are encoded by the HLA-DP, -DQ, and -DR loci (Fig. 1.2). MHC class I molecules are heterodimers composed of a membrane-bound α chain associated with a smaller molecule, called β_2-microglobulin. MHC class I molecules are expressed on all nucleated cells and generally present peptides derived from intracellular proteins. Under steady-state conditions, MHC class I molecules present self-peptides, which do not trigger an adaptive response and are critical for the inhibition of NK-cell responses. However, upon intracellular infection, MHC class I molecules can present

peptides derived from the infectious organism, which will trigger a T cell response. MHC class II molecules are also heterodimers composed of two membrane-bound chains, the α and β chain. Expression of MHC class II molecules is restricted to APCs, including DCs, monocytes, macrophages, and B cells. MHC class II molecules present peptides from antigens produced in endocytic compartments within APCs. T cells that express the CD8 co-receptor recognize antigen presented by class I MHC, and T cells that express the CD4 co-receptor recognize antigen presented by class II MHC. Finally, there is another set of MHC genes that are similar to the MHC class I, referred to as nonclassic MHC class I molecules. These genes are encoded by the HLA-E, -F, -G, and -H genes, and they generally present nonprotein antigens to a limited subset of T cells.
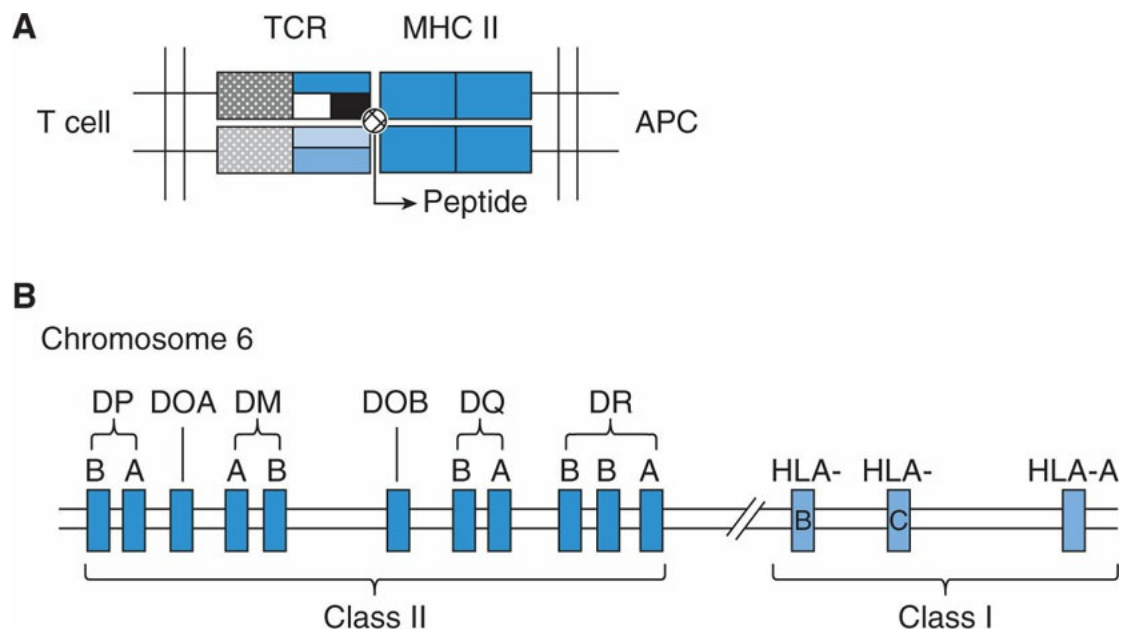
■ FIGURE 1.2 T cell receptor antigen recognition. **(A)** Presentation of peptide antigen by MHC II to the TCR. **(B)** The MHC locus. APC, antigen presenting cell; HLA, human leukocyte antigen; MHC, major histocompatibility complex; TCR, T cell receptor.

As discussed earlier, the majority of antigens recognized by the T cells are processed into peptides, which are loaded onto MHC molecules and presented to the TCR. However, superantigens are a unique class of proteins that are not processed and presented in the context of MHC molecules, but they are still recognized by T cells. Superantigens are able to bind to MHC class II molecules outside the peptide-binding region and to the variable region of the TCR β chain. Because this binding is less specific than the classic peptide–MHC–TCR interaction, superantigens are able to activate a much larger number of T cells. Many superantigens are derived from pathogenic bacteria, such as

Staphylococcus aureus.

T Cell Subsets

There are several distinct subsets of T cells, and they are generally defined by the expression of specific molecules on their surface. CD4 and CD8 T cells are the most abundant T cell subsets, the majority of which express αβ TCRs, and the commitment of a T cell to one of these two subtypes occurs during development in the thymus. Other important T cell subsets include γδ T cells and NKT cells, both of which tend to recognize and respond to nonprotein antigens. CD4 T cells are also called helper T (Th) cells, because they perform a variety of functions that stimulate other immune cells, including CD8 T cells, B cells, and macrophages. CD4 T cells produce a variety of cytokines, and they express many surface molecules that are important for their interaction with, and activation of, other immune cells. The outcome of these cellular interactions is largely dependent on the specific cytokines expressed by CD4 T cells, and CD4 T cells are often classified based on their cytokine signatures and the transcription factors they express (Table 1.2) (15). Th1 and Th2 cells were so named because they were the first two subsets to be identified and described. The other subsets were identified later, and the majority of these were named based on the primary cytokine they produced, with the exception of T follicular helper (Tfh) and regulatory T (Treg) cells, which were named based on their function.

CD8 T cells are also called cytotoxic (Tc) cells, because they express molecules such as granzyme and perforin that can directly kill target cells. Classically, CD8 T cells are associated with antiviral responses after their activation by Th1 cells, and they also play a role in the killing of cancer cells. However, it is important to note that Tc-cell subsets that express cytokine patterns similar to all the Th-cell subsets mentioned earlier have been described in the literature and likely play a role in a variety of immune responses (16).

TABLE 1.2 CHARACTERISTICS OF CD4$^+$ T CELL SUBSETS

CD4$^+$ T CELL	INDUCING CYTOKINE(s)	TRANSCRIPTION FACTOR(s)	CYTOKINES PRODUCED	FUNCTION(s)
Th1	IL-12, IFNγ	T-bet, STAT1, STAT4	IFNγ	Immunity to intracellular pathogens; autoimmunity

Th2	IL-4	GATA3, STAT6	IL-4, IL-5, IL-13	Immunity to helminths and parasites; allergy
Th9	IL-4, TGFβ	PU.1	IL-9	Autoimmunity; allergy
Th17	IL-6, IL-23, TGFβ	RORγt, STAT3	IL-17, IL-22, IL-26	Immunity to extracellular pathogens; autoimmunity
Th22	IL-6, TNF	AHR	IL-22	Immunity to pathogens, wound repair
Tfh	IL-6, IL-21	Bcl6	IL-4, IL-21	B cell help during antibody production
Treg	IL-10, TGFβ	Foxp3	TGFβ	Tolerance; immunosuppression

IFN, interferon; IL, interleukin; Tfh, T follicular helper cell; TGF, transforming growth factor; Th, helper T cells; TNF, tumor necrosis factor; Treg, regulatory T cell.

One key aspect of the adaptive immune response is its ability to form a long-lasting memory response, meaning that the specific immune response to an antigen that has been previously encountered occurs much more rapidly than the response generated during the first exposure (1). This rapid response is due to the formation of memory cells that are poised to rapidly respond to their cognate antigen, and it is the underlying mechanism for the success of vaccines. For T cells, there are two main types of memory cells, effector memory (Tem) and central memory (Tcm), that form after a naïve T cell comes into contact with the cognate antigen recognized by its TCR. Tcm cells recirculate through secondary lymphoid organs until they encounter their cognate antigen and rapidly proliferate to produce new effector T cells that can home in on sites of infection. Tem cells generally stay within the tissue and are poised to rapidly respond to pathogens at the original site of infection.

B Cell Antigen Recognition

B lymphocytes, or B cells, also develop from the CLP, but, unlike T cells, B cell development occurs exclusively in the bone marrow. Similar to T cells, however, B cell development into mature naïve B cells is dependent on the expression of a unique antigen recognition receptor, the BCR, on each B cell clone. The BCR is composed of two chains, the heavy and light chains, and two of these heterodimers are linked by disulfide bonds to form a functional BCR (Fig. 1.3). The BCR can be expressed as a surface-bound molecule or as a secreted molecule. The membrane-bound form of the BCR forms a signaling complex with CD19, which is exclusively expressed by B cells, and CD21 and CD81. The secreted form of the BCR is called an immunoglobulin, or antibody, and it plays many key roles in the control of pathogens.

Each B cell expresses only one unique BCR, and all its daughter cells will also express the same BCR and have the same antigen specificity. The heavy chain is composed of a variable region and at least two constant regions, whereas the light chain is composed of one variable region and one constant region (Fig. 1.3). The variable region of the paired heavy and light chains, also called the Fab, determines the antigen specificity of the BCR, whereas the constant region of the heavy chain, also called the Fc, determines the downstream interactions that may occur between the secreted antibody and other components of the immune system. There are five main heavy chain constant regions, or isotypes: $C\delta$, $C\mu$, $C\gamma$, $C\alpha$, and $C\varepsilon$, and two light chain constant regions: $C\kappa$ and $C\lambda$. Each BCR will use only one of the two light chains, with the κ chain generally being favored over the λ chain. The variable regions of the heavy and light chains are also generated via V(D)J recombination and junctional diversity which together have the capacity to generate at least 10^{11} unique BCRs. During development in the bone marrow, the recombined heavy chain variable region is joined only to the $C\delta$ or $C\mu$ regions, leading to the expression of immunoglobulin (Ig) D and IgM on the surface of the developing B cells.
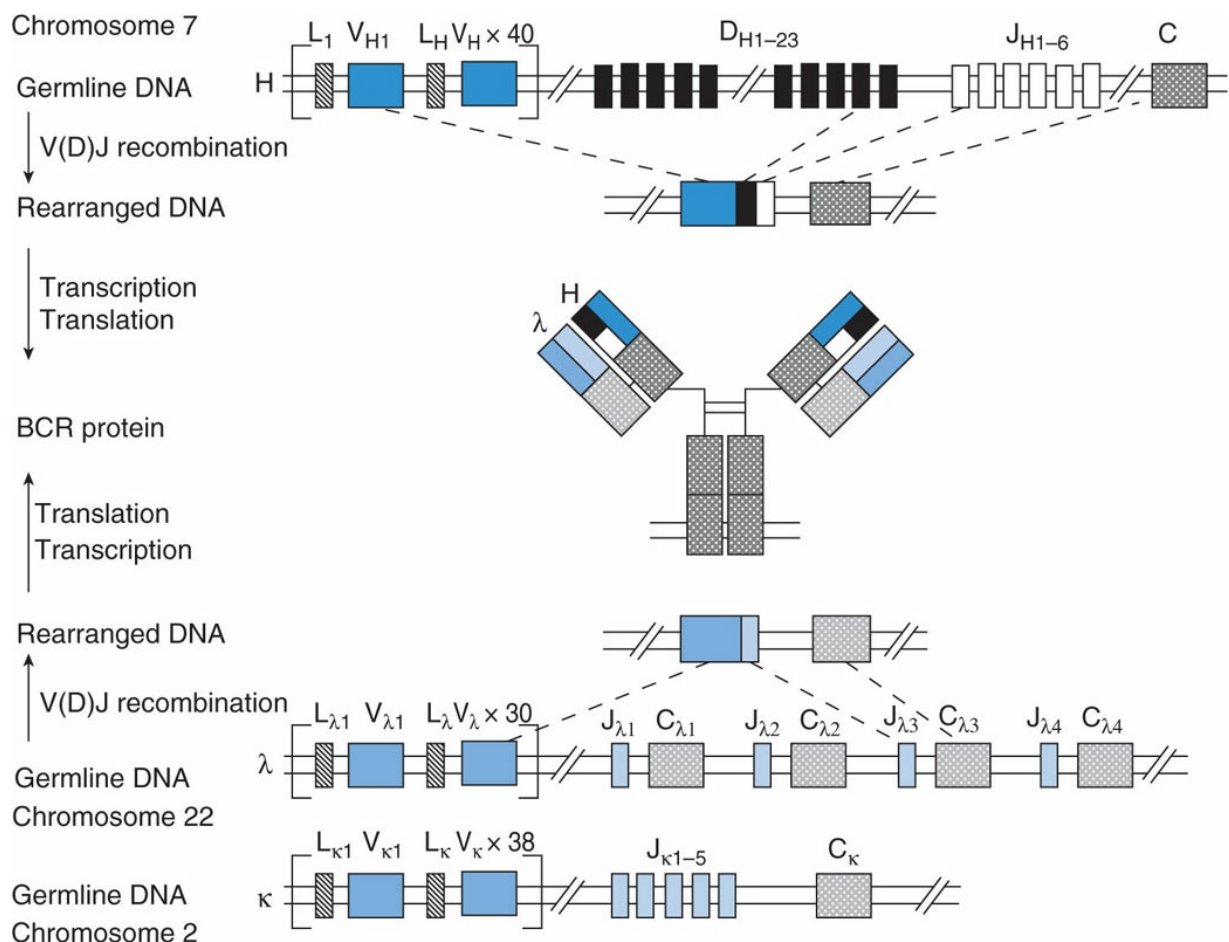
■ FIGURE 1.3 The B cell receptor.

In addition to antigen-binding specificity, variability among immunoglobulin molecules derives from three further sources: allotypes, isotypes, and idiotypes. Allotypes are determined by minor amino acid sequence differences in the constant regions of heavy or light chains, which result from slight polymorphisms in the genes encoding these molecules. Allotypic differences typically do not affect the function of the molecule and segregate within families like typical Mendelian traits. Isotypes, as already discussed, are determined by more substantial differences in the heavy chain constant regions affecting the functional properties of the immunoglobulins (Table 1.3). Finally, many antigenic determinants may be bound in more than one way, and thus there may be multiple, structurally distinct, immunoglobulins with the same antigenic specificity. These differences within the antigen-binding domains of immunoglobulins that bind the same antigenic determinants are termed idiotypes.

TABLE 1.3 HUMAN IMMUNOGLOBULIN ISOTYPES

				HALF-

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ISOTYPE	MOLECULAR WEIGHT (Da)	ADDITIONAL COMPONENTS	% OF SERUM IMMUNOGLOBULIN	LIFE(d)	FUNCTIONS
IgA					
Monomer[a,b]	160,000	—	13–19	6	Found in bodily secretions, including mucus, saliva, and tears. Prevents microbes from interacting with epithelial surfaces. In humans, subclasses are IgA_1 and IgA_2.
Dimer[b]	385,000	J chain	0.3		
IgD					
Monomer[a,b]	180,000		<1	3	Almost exclusively membrane bound on naïve B cells.
IgE					
Monomer[a,b]	190,000		<0.001	3	Majority is bound to mast cells and basophils. Cross-linking leads to degranulation and allergic responses.

IgG

Monomer[a,b] 145,000–170,000	72–80		20	Important in a wide variety of immune responses. Can activate complement and induce cell activation via Fc receptor binding. In humans, subclasses are IgG_1, IgG_2, IgG_3, and IgG_4.

IgM

Monomer[a,b] —	—	—	5–10	Found in most primary immune responses. Pentameric form is effective at activation of classical complement pathway.
Pentamer[b] 970,000	J chain	6–8		

[a]Membrane-bound form.

[b]Secreted form.

When a B cell encounters its cognate antigen it can undergo the process of isotype switching, which results in the recombined variable region being joined to a different constant region. This process is similar to V(D)J recombination in that it involves the splicing of distinct regions of the DNA together and the loss of the intervening DNA sequence. The process of isotype switching leads to the development of a B cell subclone that has the same variable region (and antigen

specificity) but a different constant region, which dictates the function of the antibody (Table 1.3). In humans, B cells can switch from IgM and IgD to IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, IgA_2, or IgE, whereas mice have only one IgA isotype. Finally, there is an additional, unique, source of generating variability in the immunoglobulin variable region, called somatic hypermutation (SHM). SHM generally occurs in germinal centers of secondary lymphoid organs during an antigen-specific B cell response, but it does not alter the antigen specificity of the immunoglobulin. Instead, random DNA bases are changed within the existing variable region, and those B cell clones that develop mutations with higher antigen affinity are selected for survival, whereas clones whose mutations do not increase antigen affinity are deleted. The result is the formation of B cell clones that express antibodies with very high affinity.

B Cell Subsets

Once B cells leave the bone marrow, they rapidly pass through two transitional stages, generally in the spleen, before they commit to one of two types: follicular or marginal zone (MZ) B cells (17). The majority of B cells will become follicular B cells termed mature naïve cells, which express both IgD and IgM on their surface. These cells traffic through secondary lymphoid organs until they encounter their cognate antigen, which results in the formation of a germinal center response. The outcome of this response is the development of both memory B cells and plasma cells. Memory B cells continue to recirculate through secondary lymphoid organs and can be rapidly reactivated if they reencounter their cognate antigen. If this happens, memory B cells can reenter the germinal center reaction and differentiate into new memory cells or plasma cells. Plasma cells are specialized, terminally differentiated B cells that secrete a large amount of antibodies to help control an invading pathogen. These cells can traffic to sites of inflammation or back to the bone marrow, where they can survive for many years and continue to secrete low levels of antibodies, and they are an important component to overall B cell memory responses.

The B cells that do not become follicular B cells instead become MZ B cells (18). These cells are well characterized in mice, where they reside in the marginal sinus of the spleen. This positions MZ B cells in an ideal location to respond to any blood-borne pathogens. MZ B cells are thought to produce low-affinity antibodies, because they do not localize to secondary lymphoid organs where the formation of germinal centers and SHM occurs. Human MZ B cells share some of these characteristics, but they can also recirculate through secondary lymphoid organs and undergo SHM and isotype switching. Another

well-characterized B cell subset in mice is the B1 B cell (19). This subset of B cells likely develops in the fetal liver from a precursor that is distinct from the CLP that gives rise to conventional follicular and MZ B cells. B1 B cells home in on the peritoneal cavity and mucosal sites, where they produce natural antibodies that are important for early pathogen recognition and tissue homeostasis. An equivalent to the B1 B cell has not been definitively identified in humans at this time.

IMMUNE RESPONSES

The Complement System

The complement system is composed of a number of serum proteins that interact with one another in a cascade to directly or indirectly kill pathogens (20). There are three pathways for complement activation: the classical pathway, the mannose-binding lectin (MBL) pathway, and the alternative pathway (Fig. 1.4). The classical pathway is initiated by the binding of certain isotypes of antibodies (IgM, IgG_1, IgG_2, and IgG_3) to antigen and then to complement component C1. The binding of C1 initiates a cascade that subsequently includes components C4 and C2, and results in the formation of the C3 convertase, which cleaves C3 into C3a and C3b, and the C5 convertase, which cleaves C5 into C5a and C5b. C3b functions as an opsonin by binding to microbial surfaces and enhancing their phagocytic destruction. C5b functions to initiate another cascade that results in the formation of the membrane attack complex, which is composed of C5b, C6, C7, C8, and C9, on a cell membrane. The membrane attack complex kills target cells by forming holes in the cell membrane and causing lysis. In addition, the anaphylatoxins formed during this cascade (C5a and C3a) are able to trigger the release of inflammatory products from endothelial cells, mast cells, and phagocytes. Although the classical pathway is activated when C1 binds to an antibody, the alternative pathway is activated by the binding of PAMPs and C3 on microbial surfaces, and the MBL pathway (also called the lectin pathway) is activated by the binding of PAMPs to mannose-binding protein (MBP). In the case of the alternative and MBL pathways, C3 or MBP, respectively, acts as soluble a PRR. The direct binding of C3 to a microbial surface initiates the alternative pathway, whereas the binding of MBP to mannose on bacterial cell surfaces initiates the MBL pathway. Both these pathways also lead to the formation of the C3 and C5 convertases and the membrane attack complex.
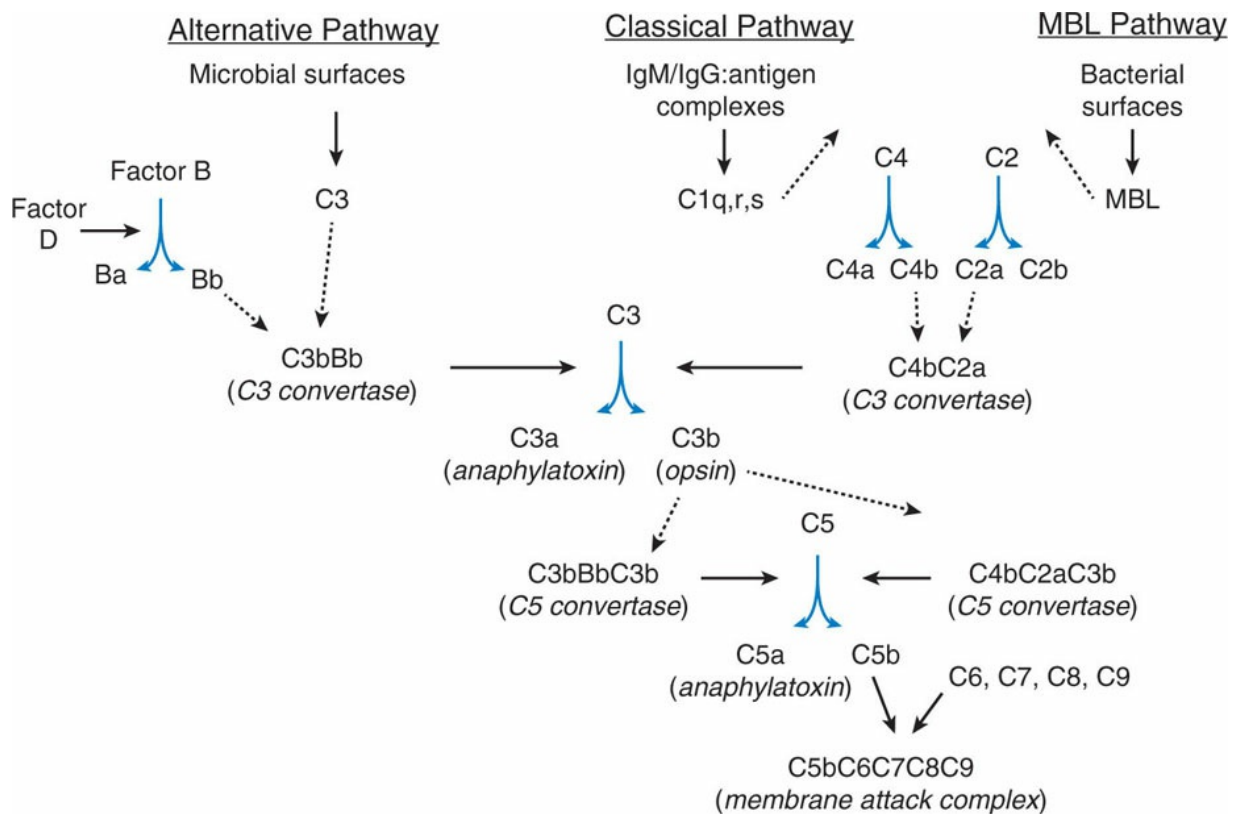
■ FIGURE 1.4 The complement system. The three complement activation pathways are shown in the top row. The classical pathway is activated by the binding of complement component C1q with antigen–antibody complexes. This triggers a cascade that leads to the formation of a C3 convertase, which cleaves C3 into C3a and C3b. C3b then binds covalently to the surface of the microbe and combines with C4b and C2a to create the C5 convertase, which cleaves C5 into C5a and C5b. C3a and C5a function to recruit phagocytes to the site of infection and promote inflammation. C5b combines with C6–C9 to form the membrane attack complex that leads to cell lysis. The lectin pathway is activated by the binding of mannose-binding lectin to carbohydrates on microbial surfaces. The lectin pathway then proceeds in the same manner as the classical pathway. The alternative pathway is activated via the spontaneous cleavage of C3 on the surface of a microbe by the C3 convertase C3bBb, and it also proceeds in the same manner as the classical pathway.

Protective Immunity against Pathogens

Protective immune responses have evolved to respond to and eliminate pathogens (1,2). These responses can generally be broken down into two categories: cell-mediated immunity and humoral immunity. Cell-mediated immune responses rely on T cells and effectors of the innate immune system to control an infection. These responses may involve the induction of an antibody

response, but the protective mechanism lies in the cellular response itself. Humoral immunity relies on the production of antibodies for the elimination of a pathogen. T cells and innate immune effector cells are also involved in humoral immune responses, but the protective mechanism lies in the production of antigen-neutralizing antibodies.

Humoral immune responses can be divided into those that require help from CD4$^+$ Th cells (T cell-dependent) and those that do not (T cell-independent), and they are directed toward extracellular antigens. T cell-dependent responses require T cells and B cells that recognize the same antigen to come together and interact in a secondary lymphoid organ, such as a lymph node. The result of this interaction is the formation of a germinal center, where the B cells undergo further activation, SHM, isotype switching, and differentiation into memory B cells or antibody-secreting plasma cells. The majority of humoral immune responses are generated in this T cell-dependent fashion to protein antigens. However, some antigens are capable of stimulating B cells to produce antibodies in the absence of T cell help. Such T cell-independent antigens are usually polysaccharides, nucleic acids, and lipids, which all contain repeating structures. Because these types of antigens are not presented in the context of MHC molecules, they are not generally recognized by T cells. These multivalent antigens are capable of binding multiple BCRs on the surface of the B cell, which provides a strong enough signal to induce B cell activation and antibody production. In some cases, cytokines produced from cells such as DCs or macrophages can also play a role in the activation of T cell-independent responses. T cell-independent antibody production is important for the immune responses against encapsulated bacteria, such as pneumococcus and meningococcus.

Regardless of the mechanism driving their production, antibodies contribute to protective immune responses in a variety of ways. Antibodies can block the attachment of microbes or their toxins to host cells, thus neutralizing their ability to enter the cells and cause damage. Antibodies bound to pathogens can also facilitate the phagocytosis of the pathogen by innate immune effector cells that express Fc receptors specific for the antibody itself. Similarly, Fc receptors on NK cells recognize cells coated in antibodies and become active to directly kill the coated cell in a process termed antibody-dependent cell-mediated cytotoxicity. Finally, as discussed earlier, antibodies play a critical role in the activation of the classical complement pathway, which can also directly kill invading pathogens.

Cell-mediated immune responses are dependent on the activation of Th or Tc cells and are generally directed against intracellular microbes that have infected host cells. Naïve Th cells are activated in secondary lymphoid organs by APCs presenting their cognate antigen in the context of MHC class II molecules. After their activation, some Th cells differentiate into effector memory cells, which can migrate back to the site of the original antigen exposure. Here, the effector memory Th cells encounter macrophages that have phagocytized the invading pathogen and are presenting antigens from the pathogen in the context of MHC molecules on their surface. The Th cells are then reactivated by this antigen and can produce cytokines (i.e., IFN-γ or IL-17) that activate the macrophage to destroy the intracellular pathogen and recruit other innate effector cells to the site to help eliminate the pathogen. Naïve CD8$^+$ Tc cells are activated in secondary lymphoid organs in a similar manner. However, when the effector Tc cell returns to the site of infection, it is capable of directly destroying cells infected by a pathogen through the production of perforin and granzyme B, or by the interaction of FasL on the Tc cell with Fas on target cells, which induces target cell death.

Tolerance

Our immune system is highly specialized to recognize and eliminate potentially harmful foreign antigens. However, every day we encounter an innumerable number of foreign antigens that pose no threat to our health or survival. These include antigens from the foods we eat, the beneficial microbes in our gut, and particles in the air, such as pollens or animal dander. In addition, our immune system must not respond to proteins expressed by our own cells (self-antigens). Immune tolerance is a key mechanism whereby our immune system is prevented from reacting to these nonharmful antigens. Tolerance mechanisms can be broadly categorized into two types: central and peripheral. Central tolerance occurs during the development of T and B cells in the thymus and bone marrow, respectively. During development, lymphocytes must pass through a checkpoint that ensures that their antigen receptors do not recognize self-antigens too strongly. Any lymphocyte clone that strongly recognizes self-antigen at this checkpoint is induced to die or become anergic. Anergic cells survive, but they are unable to respond to their cognate antigen. Thus, these potentially autoreactive clones are prevented from maturing and entering the peripheral repertoire. Peripheral tolerance is mediated by two mechanisms: suppression and anergy. Suppression is mediated by specialized T cell subsets called regulatory T cells (Tregs), which function to suppress immune responses to common antigens

encountered on a daily basis, such as foods and pollens. Some Tregs develop in the thymus as a distinct subset of T cells and are termed thymically derived Tregs (tTregs) (21). These cells are defined by their expression of the transcription factor Foxp3 and the surface molecule CD25. Other Tregs develop from T cells in the periphery and are called peripheral Tregs (pTregs). These cells may or may not express Foxp3 and are generally defined more by the cytokines they produce. tTregs rely on cell contact and production of anti-inflammatory cytokines, such as IL-10 and TGF-β, for their suppressive effects, whereas pTregs rely mainly on production of anti-inflammatory cytokines for their function. A regulatory subset of B cells (Bregs) that produce IL-10 has also been described to play an important role in the maintenance of peripheral tolerance (22). The critical role that tolerance plays in maintaining our health can be seen in patients who have defects in this system. The loss of any component of the tolerance system can lead to autoinflammatory disease and tissue damage.

Immune-Mediated Diseases

Our immune system is critical to our survival because of its role in protecting us from harmful pathogens, which usually occurs without major damage to host tissues. However, immune responses that are not properly controlled, targeted toward host cells, or triggered by harmless microbes can lead to significant tissue destruction and disease. These types of responses are termed hypersensitivity diseases and are classified into four distinct types (2).

Type I hypersensitivity, which is also termed immediate hypersensitivity, is caused by the development of Th2 responses leading to production of IgE antibodies to common environmental antigens (allergens). In susceptible individuals, exposure to an allergen, such as pollen, dust, animal dander, or some foods, leads to the development of Th2 cells that produce IL-4 and IL-13. These cytokines then lead to the activation of B cells that can undergo class switching to produce allergen-specific IgE antibodies. The IgE then binds to the high-affinity IgE receptor on mast cells. Upon allergen reencounter, the allergen binds to the mast-cell-bound IgE and triggers degranulation. As discussed previously, mast cell degranulation results in the hallmark symptoms of type I hypersensitivity, or allergic, reactions. Common diseases mediated by type I hypersensitivity reactions include allergic rhinitis, asthma, and anaphylaxis.

Type II hypersensitivity diseases are mediated by IgM and IgG antibodies that recognize proteins on the surface of host cells. Once bound, these antibodies trigger the activation of complement, which then leads to both the destruction of

the cell and the recruitment of inflammatory cells, particularly phagocytes that destroy the antibody-bound cell. Type II hypersensitivity reactions underlie a variety of clinical diseases, including myasthenia gravis, Graves disease, Goodpasture syndrome, and pemphigus vulgaris.

Type III hypersensitivity diseases are mediated by IgM and IgG antibodies specific for soluble antigens, as opposed to cell-bound antigens. The antibodies are bound to the soluble antigen from aggregates, or immune complexes, which can bind to immune cells that express Fc receptors, become deposited in a variety of tissues, and activate complement. Binding of immune complexes to Fc receptor–expressing cells leads to their activation and production of mediators that can damage blood vessel walls and further enhance deposition of more immune complexes in the tissue. Deposition of the immune complexes in the tissue can activate complement and lead to further tissue damage. Serum sickness and systemic lupus erythematosus are examples of diseases that are mediated by type III hypersensitivity reactions.

Type IV hypersensitivity reactions, which are also called delayed-type hypersensitivity because they take 24 to 48 hours to develop, are mediated by T cells. Activated Th1 or Th17 cells can directly induce the activation of macrophages and neutrophils in the affected tissue. These cells then produce proinflammatory mediators that can damage the local tissue and, in some cases, further activate T cells, creating a cycle of tissue injury and inflammation. These reactions can also be mediated by CD8$^+$ T cells and Th2 cells. Allergic contact dermatitis and poison ivy are examples of diseases that are mediated by type IV hypersensitivity reactions.

CONCLUSION

Our immune system is composed of a complex network of cells and mediators that have evolved to protect us from a vast number of different potential pathogens. The optimal functioning of this system is dependent on a balance between the need to efficiently eliminate a multitude of different pathogens and the need to minimize responses to self-proteins and harmless microbes. Any disruption in this balance results in the development of disease. Our understanding of the mechanisms involved in different immune responses has grown significantly over the past several decades, and this, in turn, has led to the development of a wide variety of effective therapies for many different diseases. However, there remains much to be learned about our immune system and how it contributes to health and disease.

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Immunology of IgE-Mediated and Other Hypersensitivity Responses

CHESTER R. ZEISS

HISTORICAL REVIEW OF IgE-MEDIATED HYPERSENSITIVITY

The year 2016 marked the 50th anniversary of the discovery of a new class of immunoglobulin, immunoglobulin E (IgE), celebrated by a wealth of publications related to the discovery and impact of this finding on the field of allergy and immunology (1,2). A brief history of the discovery of IgE follows. In 1902, Richet and Portier described the development of anaphylaxis in dogs given sea anemone toxin; subsequently, anaphylaxis was described in humans after the injection of horse serum to achieve passive immunization against tetanus and diphtheria. In 1906, Clemens von Pirquet (3) correctly predicted that immunity and hypersensitivity reactions would depend on the interaction between a foreign substance and the immune system and that immunity and hypersensitivity would have similar underlying immunologic mechanisms (3).

The factor responsible for immediate hypersensitivity reactions became a subject of intense investigation over several years. The transfer of allergy to horse dander by transfusion was reported by Ramirez in 1919 (4). In 1921, Prausnitz and Küstner (5) described the transfer of immediate hypersensitivity (to fish protein) by serum to the skin of a normal individual. This test for the serum factor responsible for immediate hypersensitivity reactions was termed the *Prausnitz–Küstner test*. Variations of this test remained the standard for measuring skin-sensitizing antibody over the next 50 years.

In 1925, Coca and Grove (6) extensively studied the skin-sensitizing factor from sera of patients with ragweed hay fever. They called skin-sensitizing antibody *atopic reagin* because of its association with hereditary conditions and because of their uncertainty as to the nature of the antibody involved. Thereafter, this factor was called *atopic reagin, reaginic antibody,* or *skin-sensitizing antibody*. This antibody clearly had unusual properties and could not be measured readily by standard immunologic methods. Major research efforts from

the 1920s through the 1960s defined its physical and chemical properties and measured its presence in allergic individuals (7,8).

In 1967, Ishizaka and Ishizaka discovered that skin-sensitizing antibody belonged to a unique class of immunoglobulin, which they called immunoglobulin E (IgE). In elegant studies using immunologic techniques, they clearly demonstrated that reagin-rich serum fractions from a patient with ragweed hay fever belonged to a unique class of immunoglobulin (9,10). Shortly thereafter, the Swedish researchers Johansson and Bennich discovered a new myeloma protein, termed *IgND*, which had no antigenic relation to the other immunoglobulin classes. In 1969, cooperative studies between these workers and Ishizaka et al. confirmed that the proteins were identical and that a new class of immunoglobulin, IgE, had been discovered (11,12).

PHYSIOLOGY OF IgE

IgE Structure and Receptors

The immunochemical properties of IgE are shown in Table 2.1, in contrast to those of the other immunoglobulin classes. IgE is a glycoprotein that has a molecular weight of 190,000 with a sedimentation coefficient of 8S. Like all immunoglobulins, IgE has a four-chain structure with two light chains and two heavy chains. The heavy chains contain five domains (one variable and four constant regions) that carry unique, antigenic specificities termed the *epsilon* (ε) *determinants* (Fig. 2.1). These unique antigenic structures determine the class specificity of this protein. Digestion with papain yields the Fc fragment, which contains the ε antigenic determinants and two Fab fragments. The Fab fragments contain the antigen-combining sites. The tertiary structure of the Fc fragment is responsible for the protein's ability to bind to the FcεRI receptors on mast cells and basophils (13).

TABLE 2.1 IMMUNOGLOBULIN ISOTYPES

ISOTYPE	NO. OF C$_H$ DOMAINS	APPROXIMATE SIZE (KDa)	ADDITIONAL COMPONENTS	PERCENTAGE OF SERUM IMMUNOGLOBULIN	APPROXIMA HALF-LIFE
IgA					
Monomer[a]	3	160,000	J chain	13–19	6

56

Dimer[b]	3	385,000	Secretory piece	0.3	

IgD

Monomer[a,b]	3	180,000		<1	3

IgE

Monomer[a,b]	4	190,000		<0.001	3

IgG					
Monomer[a,b]	3	145,000–170,000		72–80	20
IgM					
Monomer[a]	4	—	—	—	5–10
Pentamer[b]	4	970,000	J chain	6–8	—

[a]Membrane-bound form.

[b]Secreted form.

C_H, constant heavy chain; IgE, immunoglobulin E.
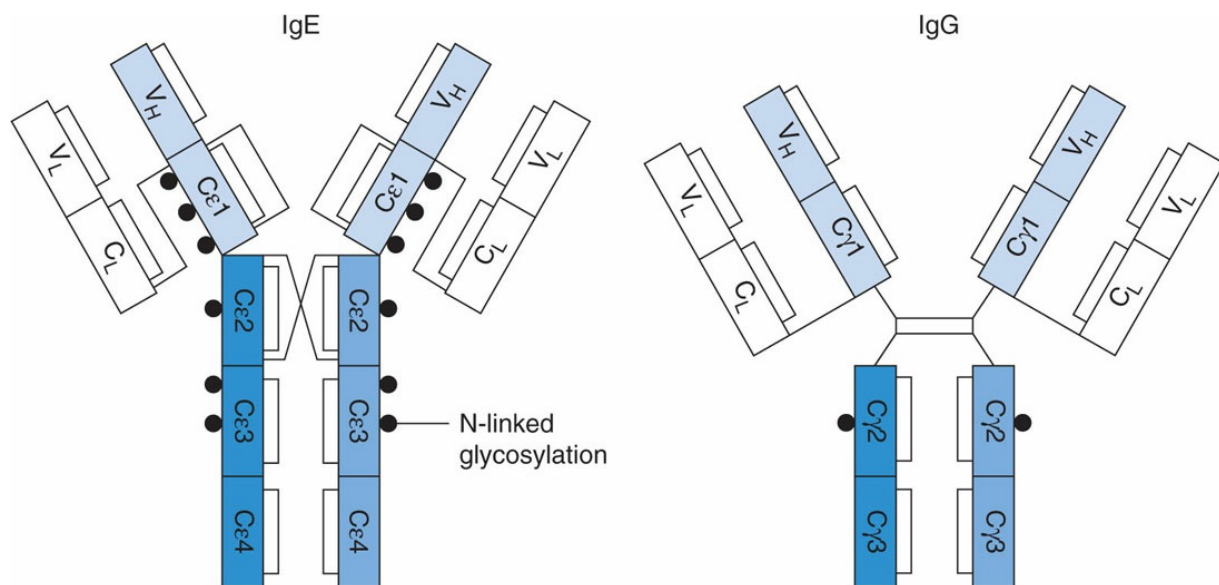
■ FIGURE 2.1 The domain structures of IgE and IgG. Schematic representations of the polypeptide and domain structures of human IgE and IgG1 showing the intra- and interdomain disulphide bridges, and sites of N-linked glycosylation. IgE, immunoglobulin E; IgG, immunoglobulin G. (From Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol*. 2008;8:205–215.)

The FcεR1 receptor is the high-affinity receptor for IgE found on mast cells, basophils, eosinophils, and human skin Langerhans cells (14). Cross-linking of high-affinity receptor-bound IgE by allergen results in the release of mediators from mast cells and basophils. Molecular biologic techniques have been used to clone the gene encoding the e chain of human IgE (ND) and to determine the site on IgE that binds to its receptor (15). Studies have localized this site to the Cε3 heavy-chain domains (16). The high-affinity receptor for IgE is composed of an α chain, a β chain, and two γ chains, and it is the α chain that binds IgE (Fig. 2.2). The crystal structure of the α chain has been determined, providing insights into the interaction of IgE with its receptor at the molecular level (17,18). The β and γ chains are involved in signal transduction when the receptors are aggregated by the cross-linking of IgE, resulting in mediator release (19). The IgE receptor on dendritic and other antigen-presenting cells (APCs) is expressed in a heterotrimeric form α,γ,γ and is called the trimeric IgE receptor (1). The capture of IgE allergen complexes by the dendritic cell trimeric IgE receptor is a highly efficient mechanism for allergen presentation to T cells (20).

A low-affinity FcεRII receptor (CD23) has been localized to B lymphocytes, monocytes, macrophages, platelets, eosinophils, and epithelial cells (21,22). The

receptor has an A form found only on B lymphocytes and a B form found on all cells expressing CD23. The molecular structure of CD23 has been delineated in detail; its binding site for IgE has three domains and in this trimeric form has a binding affinity for the IgE Cε3 region approaching that of the FceR1 receptor (18). The expression of this receptor is markedly upregulated on all cell types by interleukin-4 (IL-4) and IL-13. Binding of IgE to this receptor places IgE at the center of activation of many important effector cells and adds an additional receptor on the B cell whereby IgE can present allergen to T cells, a process called *facilitated antigen presentation* (1,20,21). The role of CD23 in regulation of the IgE response is complex, having both positive and inhibitory effects (20–22). The receptors for IgE are depicted in Fig. 2.2.

Studies have delineated the central role that IgE molecules in the circulation play in determining the number and stabilization of FcεRI receptors on mast cells and basophils (1,23,24) and, consequently, the release of mediators from these cells. After infusion of anti-IgE monoclonal antibody in allergic subjects, there is a significant reduction in serum levels of free IgE, with a dramatic fall in basophil FcεRI number and mediator release; of note, the total serum IgE is not reduced. The availability of anti-IgE monoclonal antibodies for the treatment of allergic subjects has led to a wealth of information on the complex physiology of lowering free IgE levels in serum (20). The monoclonal anti-IgE antibody, omalizumab, binds circulating IgE at the same site in the Cε3 domain as the FcεRI receptor. It therefore binds free IgE and not FcεRI receptor-bound IgE on mast cells and basophils, which would lead to mediator release (20).
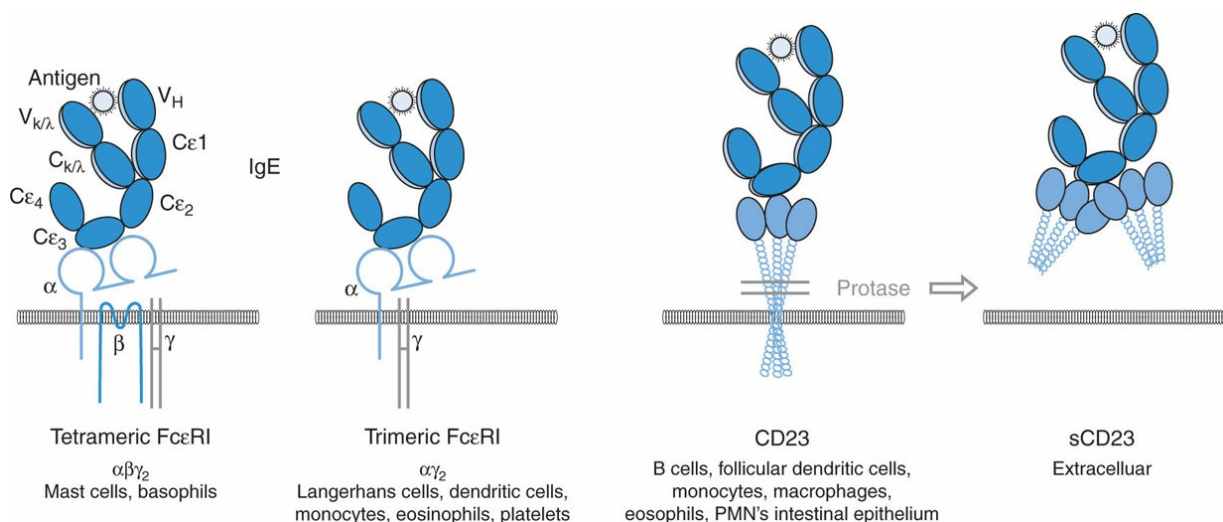
■ **FIGURE 2.2** IgE receptors. The high-affinity IgE receptor FcεRI is expressed in its tetrameric form (abg2) on mast cells and basophils. In human subjects, a trimeric form (ag2) is found on a number of lineages, including various types of professional APCs. CD23, the low-affinity IgE receptor, is broadly distributed

and is a type II transmembrane protein (N-terminus intracellular) assembled as a multimer with α-helical coiled-coil stalks terminating in IgE binding C-type lectin heads. Protease-sensitive sites in the stalks can be cleaved by endogenous proteases (including ADAM10) or exogenous proteases (including the Der p protease of dust mites). APCs, antigen-presenting cells; IgE, immunoglobulin E. (From Hans C. Oettgen. Fifty years later: emerging functions of IgE antibodies in host defense, immune regulation, and allergic diseases. *J Allergy Clin Immunol*. 2016;137:1631–1645.)

Sites of IgE Production, Turnover, and Tissue Localization

With the advent of a highly specific reagent for detecting IgE antibody against the Fc portion of IgE (anti-IgE), the sites of production of this immunoglobulin could be examined by fluorescent-labeled anti-IgE. It was found that lymphoid tissue of the tonsils, adenoids, and the bronchial and peritoneal areas contained IgE-forming plasma cells. IgE-forming plasma cells were also found in the respiratory and intestinal mucosa (25). This distribution is similar to that of IgA. However, unlike IgA, IgE is not associated with a secretory piece, although IgE is found in respiratory and intestinal secretions. The traffic of IgE molecules from areas of production to the tissues and the circulation has not been established. Areas of production in the respiratory and intestinal mucosa are associated with the presence of tissue mast cells (26). There has been renewed interest in the local mucosal production of IgE by IgE^{+} B cells. In grass- and ragweed-sensitive individuals, clear evidence of marked local production of specific IgE after allergen challenge has emerged through the use of elegant techniques to track gene activation (class-switch recombination) involved in IgE production by B cells (24). It is speculated that most IgE production occurs in mucosal tissue sites (18,27).

With the development of techniques to measure total IgE in the blood and the availability of purified IgE protein, investigators were able to study the metabolic properties of this immunoglobulin in normal individuals (28). The mean total circulating IgE pool was found to be 3.3 μg/kg of body weight, in contrast to the total circulating IgG pool of about 500,000 μg/kg of body weight. IgE has an intravascular half-life of only 2.3 days. The rate of IgE production was found to be 2.3 μg/kg/day.

It had been known for several years that the half-life of reaginic antibody in human skin as determined by passive transfer studies was about 14 days. This was reconfirmed with studies that investigated the disappearance of radiolabeled

IgE in human skin. The half-life in the skin was reported to be between 8 and 14 days (9). The basophil and mast cell-bound IgE pool needs to be investigated thoroughly, but it has been estimated that only 1% of the total IgE is cell bound. Direct quantification of specific IgE in the blood, in contrast to specific IgE on the basophil surface, indicates that for every IgE molecule on the basophil, there are 100 to 4,000 molecules in circulation (29).

IgE Synthesis

Major advances in the understanding of IgE synthesis have resulted from human and animal studies (30–36). Tada (30) studied the production of IgE antibody in rats and found that IgE antibody production is regulated by cooperation between T lymphocytes (T cells) and B lymphocytes (B cells). The T cells provide the helper function, and the B cells are the producers of IgE antibody.

In human systems, it became clear that IgE production from B cells required T-cell signals that were unique to the IgE system (31). In 1986, Coffman and Carty (32) defined the essential role of IL-4 in the production of IgE. The pathway to IgE production is complex, requiring not only IL-4 and IL-13 but also T- and B-cell contact, major histocompatibility complex (MHC) restriction, adhesion molecules, expression of FcεRII (CD23) receptors, CD40 and CD40 ligand interaction, and the terminal action of IL-5 and IL-6 (33).

IL-4 acts on precursor B lymphocytes and is involved in the class-switch recombination to ε heavy-chain production (31). Class-switch recombination requires transcription through switch regions upstream of the new constant region, DNA cleavage of single-stranded DNA at the site of transcription, and DNA repair to recombine the VDJ domain with the new Cε heavy-chain domain (1).

Class-switch recombination is a complex process that results in class switching to IgE, generating in the process switch circles and circle transcripts that signify ongoing or recent B-cell switch recombination (18,27). IL-4 and IL-13 are not sufficient to complete the switch to functional ε mRNA, and several second signals have been described that result in productive mRNA transcripts (34,35). In the absence of those signals, sterile transcripts result. A key physiologic second signal is provided by CD4^{+} helper T-cell contact. This contact signal is provided by CD40 ligand on activated T cells, which interacts with the CD40 receptor on IL-4-primed B cells and completes isotype switching to IgE (30). Several studies indicate that IgE synthesis is critically dependent on the IL-4 receptor α chain and nuclear factors such as NF-κB and Stat6 (36).

Another cytokine, interferon-γ (IFN-γ), suppresses IgE production, acting at the same point as IL-4 (33). This complex set of interactions is shown in Fig. 2.3.
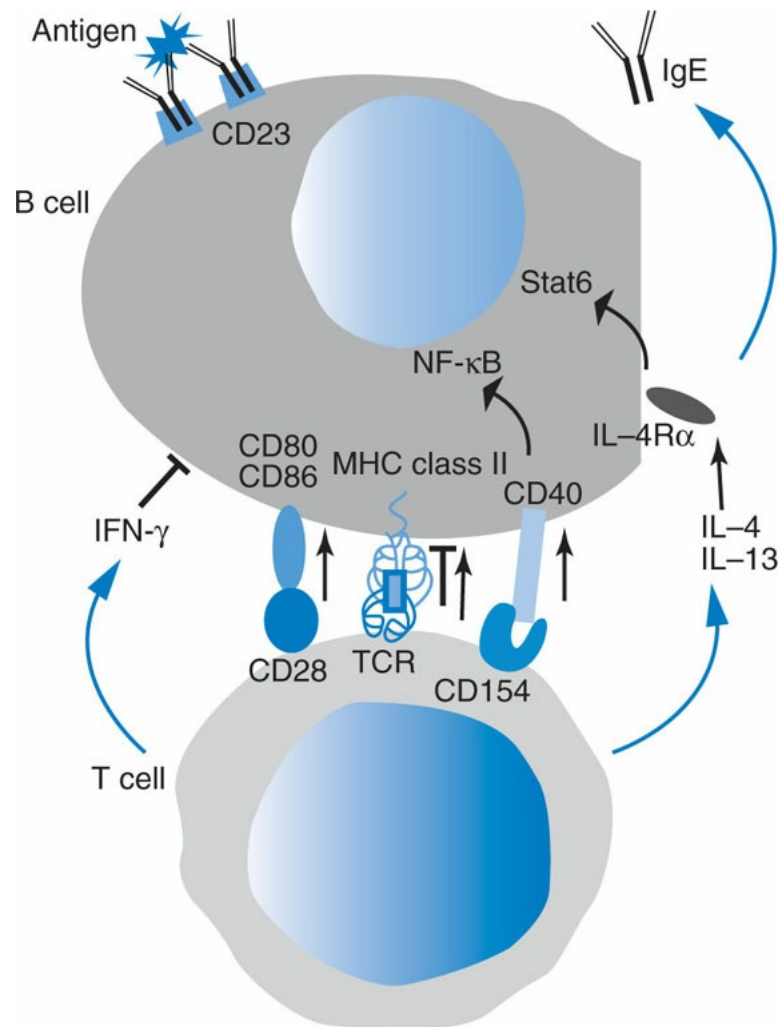
■ **FIGURE 2.3** The molecular control of the IgE response. Interleukin-4 (IL-4) and IL-13 are the most important cytokine inducers of IgE production acting at the IL-4 receptor α chain and through nuclear factor Stat6. Interferon-γ (IFN-γ) is the most important inhibitor of IgE synthesis. CD154, the T-cell ligand for CD40 on the B cell, promotes IgE transcription through nuclear factor NF-κB. Antigen presented to the T-cell receptor (TCR) by class II major histocompatibility complex molecules on the B cell initiates this complex process. IgE, immunoglobulin E. (Adapted from Cory DB, Kheradmand F. Induction and regulation of the IgE response. *Nature*. 1999;402[6760 Suppl]:B18–B23, with permission.)

During the secondary IgE response to allergen, allergen-specific B lymphocytes capture allergen by surface IgE, internalize and degrade it, and present it to T cells as peptides complexed to class II MHC molecules. This leads to T-cell–B-cell interaction, mutual exchange of cytokine and cell contact

signals, and enhanced allergen-specific IgE production. Recently, an adjuvant and immunoregulatory functions of IgE and the FcεRI receptor have been proposed (1). Mast cells and basophils residing in mucosal and skin sites produce IL-4 in response to antigen-induced IgE-FcεRI signaling. IL-4 promotes the induction of T_H2 cells and sustains their local survival. These provide the IL-4 and cognate T–B interactions critical for driving IgE class switching in mucosal B cells. Mast cells suppress T regulatory (Treg) cell expansion and function, possibly through cytokines, including IL-4 and IL-6. The trimeric FcεRI present on APCs facilitates antigen uptake for presentation to local T cells (Fig. 2.4) (1). This places IgE and mucosal mast cells and basophils at the center of an amplification loop that is allergen driven, resulting in enhanced IgE production.
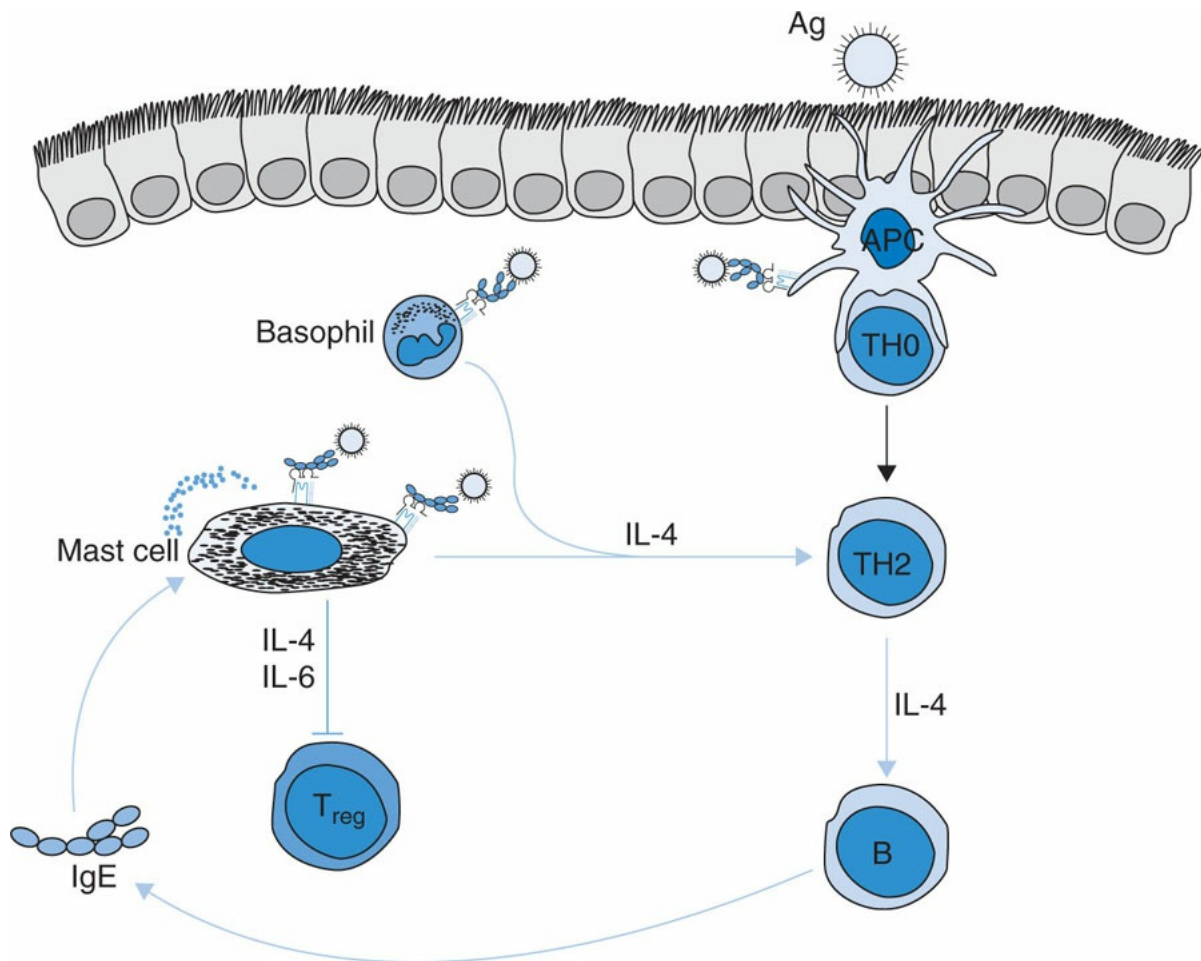
■ **FIGURE 2.4** Proposed adjuvant and immunoregulatory functions of IgE and FcεRI. Mast cells and basophils residing in mucosal and skin sites produce IL-4 in response to antigen-induced IgE–FcεRI signaling. IL-4 promotes the induction of T_H2 cells and sustains their local survival. These provide the IL-4 and cognate T–B interactions critical for driving IgE class switching in mucosal B cells. Mast cells suppress Treg cell expansion and function, possibly through cytokines,

including IL-4 and IL-6. Trimeric FcεRI present on APCs facilitates antigen uptake for presentation to local T cells. IgE, immunoglobulin E; IL-4, interleukin-4; Treg, T regulatory. (From Hans C. Oettgen. Fifty years later: emerging functions of IgE antibodies in host defense, immune regulation, and allergic diseases. *J Allergy Clin Immunol*. 2016;137:1631–1645.)

ROLE OF IGE IN HEALTH AND DISEASE

IgE in Health

The fetus is capable of producing IgE by 11 weeks' gestation. Johansson and Foucard (37) measured total IgE in sera from children and adults. They found that cord serum contained 13 to 202 ng/mL and that the concentration of IgE in the cord serum did not correlate with the serum IgE concentration of the mother, thus confirming that IgE does not cross the placenta. In children, IgE levels increase steadily and peak between 10 and 15 years of age. Johansson and Foucard illustrate well the effect that different population groups may have on the determination of *normal* levels of serum IgE. Studies of healthy Swedish and Ethiopian children showed a marked difference in mean IgE levels: Swedish children had a mean of 160 ng/mL, and Ethiopian children had a mean of 860 ng/mL (38). Barbee and coworkers (39) studied the IgE levels in atopic and nonatopic people 6 to 75 years old in Tucson, AZ. IgE levels peaked in those who were 6 to 14 years old and gradually declined with advancing age; male subjects had higher levels of IgE than did female subjects.

Several roles for the possible beneficial effect of IgE antibody have been postulated. The presence of IgE antibody on mast cells in the tissues that contain heparin and histamine points to a role for IgE in controlling the microcirculation, and a role for the mast cell as a "sentinel" or first line of defense against microorganisms has been advanced. The hypothesis is that IgE antibody specific for bacterial or viral antigens could have a part in localizing high concentrations of protective antibody at the site of tissue invasion (40,41).

The role of IgE antibody has been studied extensively in an experimental infection of rats with the parasite *Nippostrongylus brasiliensis*. IgE antibody on the surface of mast cells in the gut may be responsible for triggering histamine release and helping the animal to reduce the worm burden (42). In experimental *Schistosoma mansoni* infection in the rat, IgE is produced at high levels to schistosome antigens. IgE complexed to these antigens has a role in antibody-dependent cell-mediated cytotoxicity, whereas eosinophils, macrophages, and platelets are effector cells that damage the parasite (43). IgE and IgE immune

complexes are bound to these effector cells by the IgE FcεRII receptor, which has a high affinity for IgE immune complexes. Effector cells triggered by FcεRII receptor aggregation result in release of oxygen metabolites, lysosomal enzymes, leukotrienes, and platelet-activating factor. These observations in animals have relevance to human populations, where the IgE inflammatory cascade may protect against helminth infections (43).

IgE in Disease

The Atopic State and the T_H2 Paradigm

The term atopy was coined by Coca and Cooke in 1923 as they attempted to sort out clinical hypersensitivity states (44). Extensive evidence has accumulated that has defined the underlying immunologic basis for the atopic phenotype, that is, individuals with allergic asthma, allergic rhinitis, and atopic eczema (33). The atopic condition can be viewed as a T_H2 lymphocyte-driven response to allergens of complex genetic and environmental origins (45). The current view is that the immature T_H2 neonatal response is modified by environmental microbial exposure early in postnatal life, is modulated to a more mature and balanced T_H1 dominant pattern in normal individuals, and that the T_H2 pattern persists in atopic individuals. The reason for this persistence of the T_H2 pattern of response in atopic individuals is complex and may be related to their early response to environmental microbial exposure, the "hygiene hypothesis" (46). This interface with environmental microbial exposure has led to the investigation of the important role of the innate immune system, Toll-like receptors, and barrier epithelium in the genesis and pathogenesis of allergic disease (47,48).

Historically, the reciprocal action of IL-4 and IFN-γ on IgE production led to several studies on the T-cell origin of these cytokines. Mosmann and Coffman (49) described two distinct types of helper T cells in murine systems and defined them as T_H1 or T_H2 cells, according to the pattern of cytokine secretion. T_H1 cells produced IL-2, IFN-γ, and IL-12. T_H2 cells produced IL-4, IL-5, IL-6, and IL-10.
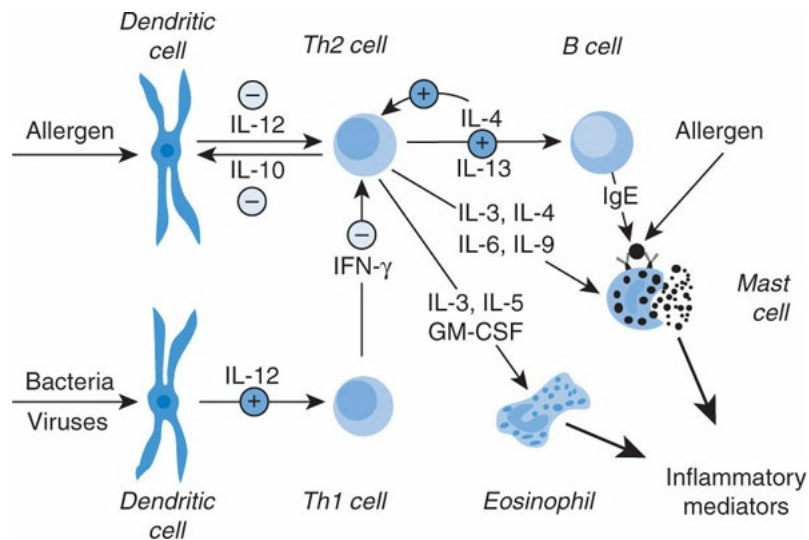
■ **FIGURE 2.5** The T_H2 cell paradigm in allergic disease. The interaction of allergen, dendritic cell, and cytokine environment causes naïve $CD4^+$ T cells to differentiate to the T_H2 phenotype with the capacity for enhanced secretion of cytokines that drive and maintain the allergic inflammatory response. The established T_H2 response downregulates the influence of T_H1 cells and the inhibitory effect of interferon-γ (IFN-γ), by the action of cytokines IL-10 and IL-4. These cytokine pathways are under complex genetic control that defines the atopic phenotype. IL-4, interleukin-4; Th, helper T cells. (Adapted from Holgate ST. The epidemic of allergy and asthma. *Nature*. 1999;402[6760 Suppl]:B2–B4, with permission.)

A significant body of evidence has further defined the role of T_H2 cells in the human atopic state related to IL-4 production, IgE synthesis, and the maturation and recruitment of eosinophils by IL-5 and the maturation of IgE B cells by IL-5 and IL-6 (33,44). T cells having the T_H2 cytokine profile have been cloned from individuals with a variety of atopic diseases (33), identified in the airway of atopic asthmatic patients, and implicated as fundamental to persistent airway inflammation in asthma (50,51).

Once a T_H2 response is established, there is downregulation of T_H1 cells by the cytokines IL-4 and IL-10. T_H1 cells are capable of downregulating T_H2 cytokine secretion through the reciprocal action of IFN-γ on T_H2 cells, a physiologic control that is abrogated by the predominant T_H2 cell response in the atopic individual (Fig. 2.5) (52).

The expression of the atopic state depends on genes that control the T_H2 response, total IgE production, and specific IgE responsiveness to environmental allergens. High serum IgE levels have been shown to be under the control of a

recessive gene, and specific allergen responses are associated with human leukocyte antigens (53). The chromosomal location and identification of these genes are under intense investigation (54,55).

The T_H1/T_H2 paradigm has been modified by newer information that includes the role of two other key T-cell populations, Tregs and T_H17 cells, that have regulatory and pro-inflammatory actions, respectively, each of which can shift the balance toward the allergic phenotype (56).

The Role of IgE in Other Disease States

The role of IgE in other disease states has continued to expand and has been recently reviewed (57). This includes new forms of anaphylaxis, eosinophilic esophagitis, fungal sensitization, and autoimmune disease (58). One emergent disease is caused by the IgE response to the lone star tick bite, *Amblyomma americanum*, with tick allergens that include an oligosaccharide determinant, galactose-α-1,3-galatose, which is also present in red meat. The IgE response to this oligosaccharide determinant induced by tick bites can lead to delayed (3 to 6 hours) food-induced anaphylaxis (59). IgE antibodies to this oligosaccharide allergenic determinant, galactose-α-1,3-galatose, are also responsible for immediate-onset, systemic anaphylaxis induced by this determinant on the Fab portion of cetuximab, a mouse–human monoclonal antibody used for the treatment of metastatic cancers (60,61).

Measurement of Total IgE

Several early studies evaluated the role of IgE in patients with a variety of allergic diseases (37–39). Adults and children with allergic rhinitis and extrinsic asthma tend to have higher total serum IgE concentrations as compared to nonatopic individuals. About half of atopic patients have total IgE concentrations that are two standard deviations above the mean of a normal control group. A significant overlap of total serum IgE concentrations in normal subjects and in patients with allergic asthma and hay fever has been demonstrated. Therefore, the total serum IgE concentration is neither a specific nor a sensitive diagnostic test for the presence of atopic disorders.

Total serum IgE has been found to be markedly elevated in some patients with atopic dermatitis (AD), and the serum IgE concentration correlates with the severity of the AD and with the presence of allergic rhinitis or asthma or both. Patients with AD without severe skin disease or accompanying asthma or hay fever may have normal IgE concentrations (62). Total IgE concentrations have

been found to be markedly elevated in allergic bronchopulmonary aspergillosis and correlate with disease exacerbations and response to therapy (63).

Measurement of Specific IgE

Since the discovery of IgE in 1967, it was possible not only to measure total IgE in the serum but also to measure IgE antibody against complex as well as purified allergens. One of the first methods described by Wide et al. (64) was the radioallergosorbent test (RAST). Allergen is covalently linked to solid-phase particles, and the latter are incubated with the patient's serum, which may contain IgE antibody specific for that allergen. After a period of incubation, the specific IgE present binds firmly to the solid phase. The solid phase is then washed extensively, and the last reagent added is radiolabeled anti-IgE antibody. The bound radiolabeled anti-IgE reflects the amounts of specific IgE bound to the allergen. The results are usually given in RAST units or in units in which a standard serum containing significant amounts of IgE specific for a particular allergen is used as a reference.

Specific IgE antibody detected by RAST in the serum of patients whose skin test results are positive to an allergen has been shown to cover a wide range. Between 100-fold and 1,000-fold differences in RAST levels against a specific allergen are found in skin-reactive individuals. In studies of large groups of patients, there is a significant correlation between the RAST result, specific IgE level, and skin test reactivity. However, individuals with the same level of specific IgE antibody to ragweed allergen may vary 100-fold in their skin reactivity to that allergen (65).

The RAST concept has been extended to the use of fluorescent and enzyme-labeled anti-IgE, which obviates the need for radiolabeled materials. Although RAST and other specific IgE measurement technologies have clarified the relationships between specific IgE in the serum and patients' clinical sensitivity, these tests do not replace skin testing with the allergens in clinical practice because skin testing is more sensitive.

It is possible to estimate the absolute quantity of specific IgE antibody per milliliter of serum against complex and purified allergens (66,67). Using one of these *in vitro* methods to measure IgE antibody against ragweed allergens, Gleich et al. (66) defined the seasonal rise and fall of ragweed-specific IgE over a one-year period. In this population of ragweed-sensitive individuals, the IgE antibody specific for ragweed allergens varied from 10 to 3,000 ng/mL. A marked rise of specific IgE level occurred after the pollen season, with a peak in October followed by a gradual decrease. Specific IgE level reached a low point

just before the next ragweed season in August (Fig. 2.6).

It was also possible to measure basophil-bound, total, and specific IgE against ragweed antigen E, now called *Amb a1*. There were between 100,000 and 500,000 molecules of total IgE per basophil (68) and between 2,500 and 50,000 molecules of specific IgE per basophil (29). The minimal ratios of ragweed allergen–specific IgE and total IgE–producing mediator release from human basophils have been determined and found to vary from 3.4/10,000 to 10/10,000. The minimal number of specific IgE molecules that were required for histamine release on the basophil surface was calculated to be 30 to 55 (69).
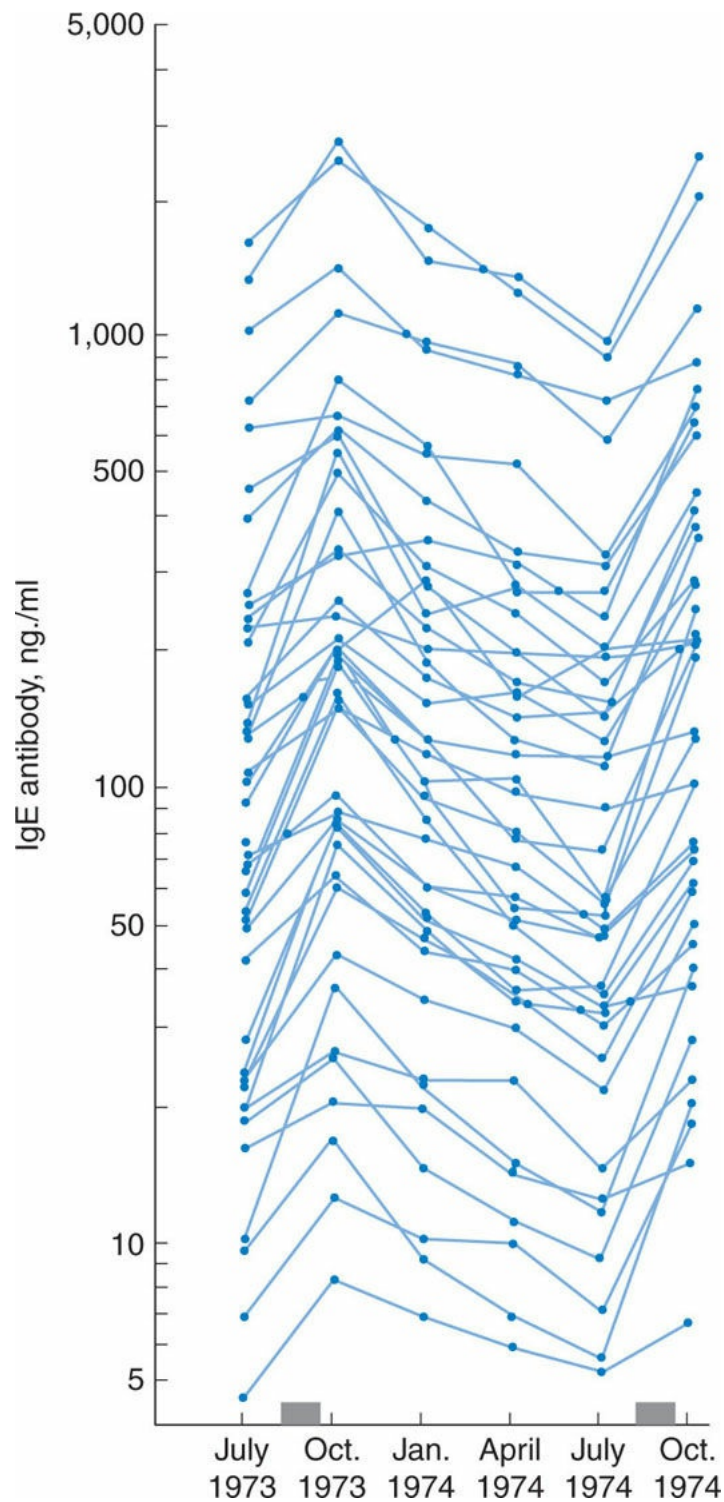
■ **FIGURE 2.6** Levels and changes of IgE antibodies to ragweed allergens in 40 untreated allergy patients. The ragweed pollination season is indicated by the *black bar* on the abscissa. IgE, immunoglobulin E. (From Gleich GJ, Jacob GL, Unginger JW, et al. Measurement of the absolute levels of IgE antibodies in patients with ragweed hay fever. *J Allergy Clin Immunol*. 1977;60:188, with permission.)

◼ OTHER HYPERSENSITIVITY RESPONSES

In 1964, Gell and Coombs classified all immunologically mediated hypersensitivity responses into four types. This classification has been a foundation for an understanding of the immunopathogenesis of clinical hypersensitivity syndromes (70). This schema depends on the location and class of antibody that interacts with antigen, resulting in effector cell activation and tissue injury.

In type I, or immediate, hypersensitivity, allergen interacts with IgE antibody on the surface of mast cells and basophils, resulting in the cross-linking of IgE, FcεRI receptor apposition, and mediator release from these cells. Only a few allergen molecules, interacting with cell-bound IgE, lead to the release of many mediator molecules, resulting in a major biologic amplification of the allergen–IgE antibody reaction. Clinical examples include anaphylaxis, allergic rhinitis, and allergic asthma.

In type II, or cytotoxic, injury, IgG or IgM antibody is directed against antigens on the individual's own tissue. Binding of antibody to the cell surface results in complement activation, which signals white blood cell influx and tissue injury. In addition, cytotoxic killer lymphocytes, with Fc receptors for IgG, can bind to the tissue-bound IgG, resulting in antibody-dependent cellular cytotoxicity. Clinical examples include lung and kidney damage in Goodpasture's syndrome, acute graft rejection, hemolytic disease of the newborn, and certain bullous skin diseases.

In type III, or immune complex, disease, IgG and IgM antigen–antibody complexes of a critical size are not cleared from the circulation and fix in small capillaries throughout the body. These complexes activate the complement system, which leads to the influx of inflammatory white blood cells, resulting in tissue damage. Clinical examples include serum sickness (after foreign proteins or drugs), lupus erythematosus, and glomerulonephritis after common infections.

In type IV, or delayed-type, hypersensitivity, the T-cell antigen receptor on T_H1 lymphocytes binds to tissue antigens, resulting in clonal expansion of the lymphocyte population and T-cell activation with the release of inflammatory lymphokines. Clinical examples include contact dermatitis (e.g., poison ivy) and tuberculin hypersensitivity in tuberculosis and leprosy.

The classic Gell and Coombs classification has been adapted by Janeway et al. (71). Subsequently, Pichler (72) further expanded the adaptation. Type II reactions have been divided into two different subtypes. Type IIa reactions are

characterized by cytolytic reactions produced by antibodies causing immune-mediated hemolytic anemia, whereas type IIb reactions are characterized by cell-stimulating reactions produced by thyroid-stimulating antibody in patients with Graves disease or antibodies to the high-affinity mast cell receptor in chronic idiopathic urticaria. The latter antibodies cause mast cell activation.

Type IV reactions are divided into four subtypes. Type IVa reactions are mediated by $CD4^+$ T_H1 cells causing classic delayed-type hypersensitivity reactions, such as allergic contact dermatitis or tuberculin reactions. Type IVb reactions are mediated by $CD4^+$ T_H2 cells, resulting in cell-mediated eosinophilic hypersensitivity as occurs in drug-induced rash with eosinophilia and systemic symptoms. Type IVc reactions are mediated by cytotoxic $CD8^+$ cells that mediate graft rejection and Stevens–Johnson syndrome. The effector cells in type IVd reactions are neutrophils, resulting in diseases such as acute generalized exanthematous granulomatosis.

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Biochemical Mediators of Allergic Reactions

ALEXANDER S. KIM AND STEPHEN I. WASSERMAN

The cells and mediators involved in diseases of immediate-type hypersensitivity have been well described. The biologically active molecules responsible have been identified, and a thorough biochemical and structural elucidation of diverse lipid mediators has been accomplished. The activity of mediator-generating cells and their diverse products has been assigned a central role in both immunoglobulin E (IgE)-mediated acute and prolonged inflammatory events. More recently, a broadened understanding of the previously implicated mediators and newer agents has occurred both in human and animal model studies. This chapter places in perspective the mediator-generating cells, the mediators themselves, and these newer concepts of their roles in pathobiologic and homeostatic events.

MEDIATOR-GENERATING CELLS

Mast cells and basophilic polymorphonuclear leukocytes (basophils) constitute the two IgE-activated mediator-generating cells (1,2). Mast cells are most closely related to mononuclear leukocytes (3) and are richly distributed in vascularized tissues in close proximity to blood vessels (particularly small arterioles and venules), smooth muscle cells, mucus-producing glands, and peripheral nerves. They are especially prominent near the host–environment interface, including the upper and lower respiratory epithelium, the bronchial lumen, the gastrointestinal mucosa and submucosa, urogenital tracts, and skin (4–7), positioning them for early recognition of pathogens and other stimuli. Mast cells are not found in avascular tissues, including cornea, cartilage, and mineralized bone (6). They develop from $CD34^+CD117^+$ bone marrow precursors through the action of stem cell factor (kit-ligand SCF), which binds to a specific receptor (c-kit, CD117) (3,8). Precursor cells exit the marrow and terminally differentiate in tissues under a variety of local influences, such as interleukin 3 (IL-3), IL-4, IL-6, IL-9,

IL-10, and factors from fibroblasts (9,10), but are inhibited by transforming growth factor β (11).

Migration of mast cell progenitors to specific tissues such as the gastrointestinal tract and lung depends on targeted interactions of integrins, adhesion molecules, chemokines, growth factors, and cytokines. Mast cell migration to the gastrointestinal tract involves the binding of the integrin $\alpha_4\beta_7$ to mucosal addressin cell adhesion molecule-1 or to vascular cell adhesion molecule 1 (VCAM-1). The chemokine receptor CXC chemokine receptor 2 (CXCR2) has also been demonstrated to be involved with mast cell migration to the intestines (12). Mast cell progenitors typically are recruited to the lung during allergen-mediated inflammation via $\alpha_4\beta_7$ and $\alpha_4\beta_1$ interactions with VCAM-1 and CXCR2 (13).

Mast cells are large (10 to 15 µm diameter) and possess a ruffled membrane, numerous membrane-bound granules (0.5 to 0.7 µm in diameter), mitochondria, a mononuclear nucleus, and scant rough endoplasmic reticulum. Ultrastructurally, human mast cell granules display whorl and scroll patterns (14). Mast cells are heterogeneous, and both connective tissue (MC_{TC}) and mucosal types (MC_T) have been recognized (15). Connective tissue mast cells (MC_{TC}) dominate in the skin and can be distinguished from the mucosal type by expressing CD-88 (C5aR) on their cell surface. MC_{TC} are also found in lesser quantities in the gastrointestinal system, conjunctivae, perivascular tissues, bronchial smooth muscle, and glandular region of lungs (16). In the asthmatic lung, elevated levels of MC_{TC} are found in the smooth muscle (17,18). This mast cell type expresses tryptase, chymase, cathepsin-G-like protease, and carboxypeptidase A in the granules and produces IL-4 and IL-13 (19). Mucosal-type mast cells (MC_T) predominate in the lamina propria of the gastrointestinal tract as well as the peripheral airways, alveolar septa, and epithelium of the lung. MC_T cells predominantly express tryptase and produce IL-5 and IL-6 (19–21). A third mast cell type was described in asthma and eosinophilic esophagitis and found to express tryptase and carboxypeptidase A3 (22,23). Although mast cells are classically phenotyped based on protease content as MC_T and MC_{TC}, there is increasing evidence that interphenotype variability and plasticity exist and depend on the microenvironment in which they reside. The growth factor and cytokine environment has been demonstrated *in vitro* to regulate mast cell phenotype induction in both murine and human studies, but the clinical relevance has yet to be determined. There appear to be numerous diverse subphenotypes

within the two stereotypical mast cell types that differ with respect to microlocalization, function, and structure (13,24).

A c-kit mutant mouse has been developed using the W-*sash* mouse (Kit$^{W-sh/W-sh}$) producing an experimental mast cell–deficient mice model that, unlike prior c-kit knockout models, can successfully reproduce (25,26) and has no other leukocyte deficiencies and should thus be helpful in further describing the mast cell's role in inflammation. More recently, proteomic analysis of releasates from IgE-mediated activation of murine bone marrow–derived cultured mast cells and murine peritoneal cell–derived mast cells has suggested that differential proteolysis underlies the regulation of mediator production. Understanding how differential protease activity can alter the mediator profile of mast cells in murine models could lead to an enhanced understanding of human homeostasis vis-à-vis mediator production in response to IgE-mediated mast cell activation (27).

Basophils, most closely related to eosinophils, are circulating leukocytes whose presence in tissue is unusual except in disease states (28). They originate in the bone marrow and constitute 0.1% to 2.0% of the peripheral blood leukocytes. Basophils possess a polylobed nucleus and differ from mast cells in their tinctorial properties, their relatively smooth cell surface, and their granule morphologic makeup, which is larger and less structured than that of the mast cell. Their growth is responsive, not to SCF, but rather to IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF).

Other mediator-generating cells include platelets, which express FcεRI (29) and release serotonin, RANTES, platelet-activating factor (PAF), and platelet factor 4 as well as cytokines and chemokines. Their role has been imputed from mouse studies of anaphylactoid shock in mast cell–deficient animals (30). Eosinophils have been suggested to play both a proinflammatory role, through release of granule-associated proteins, and an anti-inflammatory role, through the metabolism of vasoactive mediators (Table 3.1) (31).

TABLE 3.1 HUMAN MAST CELL SUBTYPES

FEATURE	MCT$_C$ CELL	MCT$_T$ CELL
Structural features		
Grating/lattice granule	++	−

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	Poor	Rich
Scroll granules	Poor	Rich
Tissue distribution		
Skin	++	−
Intestinal submucosa	++	+
Intestinal mucosa	+	++
Alveolar wall	−	++
Bronchi	+	++
Nasal mucosa	++	++
Conjunctiva	++	+
Mediator synthesized		
Histamine	+++	+++
Chymase	++	−
Tryptase	++	++
Carboxypeptidase	++	−
Cathepsin G	++	−
LTC_4	++	++
PGD_2	++	++

TNF-α	++	++
IL-4, IL-5, IL-6, IL-13	++	++

IL, interleukin; LTC, cysteinyl leukotriene; MC$_T$, mucosal type mast cells; MC$_{TC}$, connective tissue mast cells; PGD$_2$, prostaglandin D$_2$; TNF-α, tumor necrosis factor α.

Adapted from Krishnaswamy G, Chi DS. The human mast cell: an overview. *Methods Mol Biol*. 2006;315:16; Table 1. ©Humana Press Inc.

A rapidly expanding area of type 2 immune research involves group 2 innate lymphoid cells (ILC2s), formerly called natural helper cells, innate helper 2 cells, and nuocytes. ILC2s are known as lineage-negative lymphocytes devoid of any T, B, or natural killer (NK) cell surface markers; they require the master transcription factor GATA3. Similar to mast cells, ILC2s are thought to play a role not only in allergic inflammation but also in homeostasis. Activation of ILC2s can occur via the cytokines IL-25 and IL-33, the latter which has also been shown to activate mast cells (32). IL-33, a member of the IL-1 superfamily, binds to ST2 expressed on both ILC2s and mast cells, and plays a role in their activation and proliferation (33). Once activated, ILC2s are capable of significant production of Th2 cytokines, including IL-4, IL-5, and IL-13. ILC2s are also stimulated by lipid mediators, most notably prostaglandin D2 (PGD$_2$) and cysteinyl leukotrienes (LTC$_4$, LTD$_4$, and LTE$_4$) as well as tumor necrosis factor (TNF)-like ligand 1A to produce IL-4, IL-5, IL-6, IL-9, IL-13, and GM-CSF. Lipid mediators have been long associated with type 2 inflammatory conditions, including asthma and chronic rhinosinusitis (CRS) (32).

ACTIVATION OF MAST CELLS AND BASOPHILS

The IgE-mediated response via FcεRI receptor cross-linking is the principal mechanism underlying type I immediate allergic reactions (7). Mast cells and basophils possess numerous high-affinity intramembranous receptors (FcεRI) for the Fc portion of IgE. The number of such receptors is upregulated and their stability enhanced by exposure of the mast cell or basophil to increased amounts of IgE (34). Aggregation of two or more of these FcεRI receptors with antigen cross-linking of receptor bound, antigen-specific IgE molecules leads to receptor activation and complex signal transduction, thereby leading to the release of mediators from mast cells and basophils (35). There is, however, increasing evidence that antigen specificity is not always required for IgE mast cell

responses such as FcεRI upregulation and cytokine production and has been referred to as the monomeric IgE response. Monomeric IgE-induced mediator release may depend on SCF, but the exact mechanism is still unknown (36).

Preformed mediators from mast cell cytoplasmic granules are released immediately and include histamine, neutral proteases, a small proportion of total cytokines, and proteoglycans. Unstored mediator synthesis is initiated in minutes and includes the production of lipid membrane–derived arachidonic acid, prostaglandins (PGD_2), PAF, and leukotrienes (LTB_4 and LTC_4). Chemokine and cytokine products are unstored and are produced within hours of the initial stimulus, and their release can continue for days (37). Mast cell responsiveness may be heightened by exposure to SCF or other cytokines (7,38,39), whereas basophils are primed to respond by GM-CSF, IL-1, IL-3, and IL-5 (40). Other important secretagogues include a family of histamine-releasing factors (41) and complement fragments C3a and C5a, the latter of which have not shown to be necessary to mount an anaphylactic episode (42). The coagulation cascade and kallikrein–kinin contact system have also been implicated to be involved because of the reported decreases in fibrinogen, factors V and VIII and factor XIIa-c1 inhibitor complexes, high-molecular weight (HMW) kininogen, and kallikrein-C1 that have been seen (43).

The FcεRI receptor, a member of the immunoglobulin superfamily, is composed of one extracellular subunit α, which binds to IgE, and two intracellular subunits β and γ, which are associated with enzymes and are essential in the subsequent signal transduction upon the activation of mast cells and basophils. FcεRI receptor bridging is followed by phosphorylation of the immunoreceptor tyrosine–based activation motifs of the β and γ subunits which acts as a scaffold to allow the binding of additional signaling molecules, the most important of which is the protein tyrosine kinase Syk. Syk binds, via the γ subunit of the receptor, becomes phosphorylated, and leads to the phosphorylation of several downstream proteins, directly and indirectly (35). The net result of this signaling is an increase in intracellular calcium, protein kinase C translocation, G-protein activation, and cyclic adenosine monophosphate generation. At the same time, membrane phospholipids are metabolized to generate monoacylglycerols, diacylglycerols, and phosphorylated inositol species, which facilitate protein kinase C function and liberate Ca^{2+} from intracellular sites. While these biochemical events are underway, adenosine triphosphate (ATP) is catabolized, and adenosine is liberated which further activates a mast cell adenosine receptor to enhance granule release. Finally, the cell gains control over mediator release, the process stops, and the cell

regranulates (44).

Although initiated at the time of IgE and antigen activation, the generation of cytokines is expressed over a time frame of hours to days. Both mast cells and basophils are important sources of a variety of inflammatory cytokines, as described later. After the initiating event of allergen binding, cytokine synthesis proceeds through activation of signaling pathways such as the STAT and nuclear factor-κB (NF-κB)-regulated processes, with gene transcription evident within hours and protein secretion occurring subsequently (45).

Recent work involving microRNAs (miRNAs) has added further complexity to mast cell activation. MiRNAs are noncoding RNA segments capable of post-translational regulation of gene expression. Although the role of miRNAs has been well established in many immunologic disorders, their function in the context of mast cell activation is not well known. One study demonstrated that after antigen-specific IgE-mediated mast cell activation, MiR212-22, was found to be upregulated. Another miRNA, MiR-142-3p, was found to induce FcεRI-mediated mast cell degranulation (46). There are several maintained databases available for bioinformatics analysis that can predict binding sites for specific miRNAs. There have been several potential target genes identified involved with the signaling pathways of IgE-mediated mast cell activation and may in the future lead to the development of novel therapeutic agents for IgE-mediated allergic diseases.

Mast cell activation also occurs via alternative pathways, including complement, contact system, neuropeptides, cytokines, proteases, drugs, and toll-like receptors. Recently, a novel human mast cell surface G-protein-coupled receptor MRGPRX2, was identified as the receptor for several peptidergic drugs, including fluoroquinolones, bradykinin B_2 receptor antagonists, and neuromuscular blocking agents. This receptor has been found in high levels in skin MC_{TC} and in low levels in lung MC_T (47). The mechanism appears to involve downstream activation of the phospholipase-Cγ pathway, leading to mediator release and eicosanoid production (48). Inhibition of this receptor may prevent anaphylactic events, and further research is needed to explore this possibility. Mast cells also possess a receptor for IgG, FcγRII, which can modulate mediator release (49), and these cells also respond to endotoxin through engagement of a toll-like receptor complex. The presence of these additional modulatory pathways suggests that mast cell and basophil mediators participate in inflammatory conditions in which IgE may not be present. Murine models suggest further mechanisms in the activation and signaling of mast cells

and basophils. Zinc has been implicated in inducing FCεRI-dependent mast cell degranulation, cytokine production (IL-6 and TNF-α), NF-κB activation, and, possibly, protein kinase C plasma membrane translocation (50). Sensory skin nerves may augment mast cell–derived inflammation by releasing neuropeptides such as substance P and calcitonin gene-related peptide in this setting, with less mast cell driven inflammation being seen in denervated skin (51). A protein of the regulator of G-protein signaling (RGS) family, RGS13, has been shown to halt normal signal transduction downstream of FcεRI by blocking PIP3 phosphorylation from occurring in mast cells, suggesting it may have a role in their homeostasis (52). A human Ig fusion protein, Fcγ-Fcε (GE2 protein), has been shown to inhibit FcεRI signaling by cross-linking FcεRI with FcγRIIb, a negative regulatory molecule (53,54). Its role in the basal regulation mast cell and basophil activity has not been fully evaluated.

Human basophil activation can be detected using cell surface markers CD63 and CD203c. In the resting state, human basophils express CD63 on the membranes of secretory granules, and CD203c is expressed in vesicular membranes after activation. When cross-linking of FcεRI occurs as in anaphylaxis, both secretory granules and vesicles migrate to the cell surface and can be detected using flow cytometry. Other candidate surface markers studied have been CRTH2, CD123, and CCR3. The basophil activation test is both sensitive and specific for IgE-mediated responses to pollens, foods, hymenoptera venom, drugs, and natural rubber latex and may play a future role as a marker for monitoring immunotherapy responses (55).

THE ROLE OF MAST CELLS AND BASOPHILS IN ILC2 RESPONSES

The interrelationship between mast cells and ILC2s has been investigated in murine and human studies, and colocalization has been demonstrated in the mouse dermis and human lung. As mentioned earlier, mast cells can produce lipid mediators capable of activating ILC2s, including PGD_2, which plays an important role in ILC2 chemotaxis in humans via the PGD_2 receptor CRTH2 on the ILC2 membrane (56). In turn, the IL-9 produced by ILC2s allows for tissue accumulation of mast cells (57).

The mechanism of immunoregulation of ILC2 and mast cell activation has not been fully elucidated. In a house dust mite–derived protease study, mast cells suppressed ILC2-mediated responses. Mast cells stimulated by IL-33 were able to promote regulatory T-cell expansion and IL-10 production via IL-2, ultimately

constricting ILC2-mediated inflammation. Conversely, the aforementioned c-kit mutant mouse (Kit$^{W-sh/W-sh}$) was found to have protease-induced lung inflammation associated with decreased regulatory T cells (Tregs) (58). A murine study examining allergic skin disease found differential functioning of ILC2s *in vivo* depending on whether cells were in steady state or stimulated. ILC2s in steady state served an immunoregulatory role and induced mast cell suppression via IL-13, but when activated, became proinflammatory and promoted mast cell activation (59).

The link between ILC2s and basophils has been described in atopic dermatitis and allergic asthma murine studies. In atopic dermatitis, increased clusters of basophils and ILC2s have been demonstrated in lesional skin compared to healthy controls. Upon stimulation by IL-33 or thymic stromal lymphopoietin (TSLP) released in response to barrier disruption, basophils regulate ILC2 responses by producing IL-4, which binds to its receptor IL-4Rα on neighboring ILC2s and promotes ILC2 accumulation and proliferation (60). ILC2s have also been shown to contribute to type 2 lung inflammation in response to allergens, such as alternaria and house dust mite (32). Basophils, via their production of IL-4, have been demonstrated to promote lung ILC2 proliferation and expression of IL-5, IL-9, and IL-13 in ILC2s (60) based on a murine model involving basophil-derived IL-4-deficient mice. These IL-4-deficient mice were noted to have decreased lung ILC2 activation and decreased IL-5 and IL-13 production (61).

IMMUNOMODULATION OF MAST CELLS

Homeostatic mechanisms known to modulate mast cell activation in allergic disease involve the microbiota, inhibitory receptors, regulatory cells, and cytokines. Mast cells express pattern recognition receptors responsible for detecting danger signals from pathogens such as bacteria and generating an immune response. The sialic acid binding immunoglobulin-type lectins (Siglecs) have been demonstrated to suppress IgE-mediated degranulation of mast cells. Additional research has identified bacteria with sialic acid mimics capable of binding to inhibitory Siglec receptors.

There is emerging literature examining the ability of nonpathogenic and pathogenic microbes to modulate mast cell activity with respect to allergic disease. The nonpathogenic microbes of the microbiota may play an important role with respect to mast cell immunomodulation. Murine research involving nonpathogenic *Escherichia coli* demonstrated the inhibition of mast cell

activation via preclusion of granule fusion with the mast cell membrane. Another commensal organism *Lactobacillus* has also been shown to inhibit IgE-mediated mast cell activation in mice, although the underlying mechanism is currently unknown (62). It has been theorized that the suppression of mast cell activity may occur through different mechanisms depending on the strain such as via pattern recognition receptors or calcium-activated potassium channels (63).

Regulatory T cells (Tregs) are well-established mediators of immune tolerance in allergic disease, but, only recently, the evidence in murine studies has demonstrated a linkage between the microbiome and mast cells, Tregs, and their immunosuppressive cytokines, such as IL-10. Strains of *Lactobacillus rhamnosus* have been shown to dampen airway responses associated with increased Tregs (FoxP3$^+$). The mechanism of mast cell degranulation inhibition appears to involve OX40/OX40 ligand (62).

A clearer understanding of the interplay between mast cells and the microbiota in humans is essential to devising new strategies in attenuating allergic disease. Whether advances in microbiome research and technology will lead to novel and therapeutic uses for probiotics in allergic disease remains to be seen.

MEDIATORS

Whatever their final metabolic interrelationships, the early biochemical processes lead to the generation of a heterogeneous group of molecules termed *mediators*. Some mediators are preformed and are stored in the granules of the cell, whereas others are generated only after cell activation and originate in the cytosol or membrane. Mediators are classified in this chapter by their proposed actions (Tables 3.2 and 3.3), although some mediators subserve several functions.

Spasmogenic Mediators

Histamine, generated by decarboxylation of histidine, was the first mast cell mediator to be identified, and it is the sole preformed mediator in this functional class. It is bound to the proteoglycans of mast cell and basophil granules (5 and 1 mg/10^6 cells, respectively) (64,65). Histamine circulates at concentrations of about 300 pg/mL with a circadian maximum in the early morning hours (66). Histamine excretion exceeds 10 mg/24 hours; a small fraction is excreted as the native molecule and the remainder as imidazole acetic acid or methyl histamine. Histamine interacts with specific H_1, H_2, H_3 and newly discovered H_4 receptors

(67–69). The H_4 receptor has low homology with the other histamine receptors but shares the most with the H_3 receptor with 35% amino acid homology (69). Antihistamines specific for the H_1 and H_2 receptors do not bind to the H_4 receptor (70).

TABLE 3.2 MAST CELL VASOACTIVE AND SPASMOGENIC MEDIATORS

MEDIATOR	OTHER ACTIONS
Histamine	Alters cell migration
	Generates prostaglandins
	Increases mucus production
	Activates suppressor T lymphocytes
Platelet-activating factor	Activates platelets
	Attracts and activates eosinophils
Prostaglandin D_2	Prevents platelet aggregation
	Alters cell migration
Sulfidopeptide leukotrienes (C_4, D_4, E_4)	Generates prostaglandins
Adenosine	Prevents platelet aggregation
	Enhances mediator release
	Inhibits neutrophil superoxide production

TABLE 3.3 MAST CELL MEDIATORS AFFECTING CELL MIGRATION

MEDIATOR	CELL TARGET
High-molecular weight NCF	Neutrophils
ECF-A	Eosinophils

ECF oligopeptides	Eosinophils (secondary mononuclear)
T-lymphocyte chemotactic factors	T cells
Histamine	Nonselective
PGD_2	Eosinophils and neutrophils
Leukotriene B_4	Neutrophils
Leukotriene E_4	Eosinophils
PAF	Eosinophils and neutrophils
Lymphocyte chemokinetic factor	T and B cells

ECF-A, eosinophil chemotactic factor of anaphylaxis; NCF, neutrophil chemotactic factor; PAF, platelet-activating factor; PGD_2, prostaglandin D_2.

All of the histamine receptors are G-protein-coupled receptors. H_1 receptors utilize G_q proteins, leading to phospholipase C activation, inositol phosphate production, and, eventually, calcium mobilization (71). H_2 receptors use $G\alpha_S$ proteins, causing an increase in cyclic AMP. H_3 receptors use $G\alpha_{i/o}$, causing inhibition of cAMP, increasing calcium mobilization, and activating MAP kinases and ion channels (72). H_4 receptors seem to work through pertussis toxin–sensitive $G\alpha_{i/o}$ proteins, which signal through increases in intracellular calcium; however, other pathways have been described (73).

H_1 receptors predominate in the skin and smooth muscle; H_2 receptors are the most prevalent in the skin, lungs, and stomach and on a variety of leukocytes; H_3 receptors predominate in the brain; H_4 receptors appear to be present on mast cells, basophils, eosinophils (74,75), dendritic cells, CD4^{+} effector T cells (at low levels) (75), and CD8^{+} effector cells (76) and may be present on neutrophils and monocytes (70) as well as on lung parenchymal cells (77). The biologic

response to histamine reflects the ratio of these receptors in a given tissue. Increased levels of histamine have been reported in the blood or urine of patients with physical urticaria, anaphylaxis, systemic mastocytosis, and antigen-induced rhinitis and asthma (78). H_1 histamine effects include the contraction of bronchial and gut musculature, vascular permeability, pulmonary vasoconstriction, and nasal mucus production (79,80). By its H_2 pathway, histamine dilates respiratory musculature, enhances airway mucus production, inhibits basophils and skin (but not lung) mast cell degranulation, and activates suppressor T lymphocytes. Both H_1 and H_2 actions are required for the full expression of pruritus, cutaneous vasodilation, and cardiac irritability (67). The H_3 actions of histamine suppress central nervous system histamine synthesis. The H_4 actions of histamine include eosinophil chemotaxis, cell shape change, and upregulation of adhesion molecules, the induction of mast cell chemotaxis toward a histamine gradient (74,75), and an increase in cytokine production from dendritic and T cells (77,81). Studies using the H_4 receptor antagonist JNJ 7777120 help support these findings (76,82), and H_4 KO mice suggest that the H_4 receptor has a role in allergic airway inflammation through activation of $CD4^+$ T cells (83). It is also thought possible that this receptor is an important factor in pruritus.

Platelet-Activating Factor

PAF is a lipid identified structurally as 1-0-alkyl-2-acetyl-sn-glycerol-3-phosphocholine (84). It is a metabolic product of phospholipase A2 and acetyltransferase and works through G-protein-coupled receptors (85). PAF is primarily secreted by mast cells in IgE-mediated reactions; by basophils in IgG-mediated reactions; by phagocytes such as monocytes, macrophages, and neutrophils; by eosinophils in response to chemotactic factors; and by endothelial cells because of various other stimuli, including thrombin and IL-1 (84,86). Functional receptors are found on platelets, monocytes, neutrophils, and eosinophils (85). Degradation of PAF occurs by the action of acetyl hydrolase to remove acetate from the sn-2 position.

PAF causes aggregation of human platelets, wheal-and-flare permeability responses, eosinophil chemotaxis (87), smooth muscle contraction, and increased vascular permeability (86). PAF has the ability to induce histamine release from basophils and mast cells, thus causing eosinophils and neutrophils to degranulate and increase LTC_4 formation by eosinophils (85). The receptor for PAF, PAFR,

has been found to be preferentially expressed on MC_T cells, which is in agreement with evidence that PAF-mediated histamine release occurs on peripheral blood and lung mast cells but not skin mast cells (84). PAF also contracts pulmonary and gut musculature, induces vasoconstriction, and is a potent hypotensive agent. Effects mediated by PAF also include pulmonary artery hypertension, pulmonary edema, an increase in total pulmonary resistance, and a decrease in dynamic compliance. In addition, PAF is capable of inducing a prolonged increase in nonspecific bronchial hyperreactivity *in vivo* (88).

Recently, the relative activity of PAF acetylhydrolase (PAF-AH) has been directly and inversely linked to the severity of food and venom anaphylaxis (89,90). PAF-AH has been found to form complexes with low-density lipoprotein (LDL) in the circulation and has raised the question whether decreasing LDL levels will increase the risk of anaphylaxis (84). Murine studies have investigated PAF antagonists, and animal models have demonstrated significant reductions in food anaphylaxis severity as well as synergistic responses of PAF antagonist and antihistamine administration (84). Definitive strategies employing this information to target treatment or to stratify patients at risk for anaphylaxis remain to be elucidated.

PAF has also been demonstrated to be involved with allergic rhinitis and asthma pathogenesis. Nasal challenge with PAF leads to increased nasal obstruction and nasal airway resistance, and inhalation challenge results in mucus hypersecretion, an inflammatory response, bronchoconstriction, and impairment of gas exchange. There is some evidence that the 5-lipoxygenase inhibitor can protect against lung hyperreactivity, leading to the possibility that leukotrienes and thromboxane may be involved in the respiratory responses of PAF (84).

Nitric Oxide

Nitric oxide (NO) is a radical derived from L-arginine by nitric oxide synthase (NOS), upon histamine binding to H_1 receptors, involved in smooth muscle relaxation and hypotension and shock related to anaphylaxis (91). NO activates guanylate cyclase, leading to vasodilation and the production of cyclic guanosine monophosphate. Three types of synthases have been discovered: inducible NOS (iNOS), neuronal NOS (n-NOS), and endothelial NOS (e-NOS). e-NOS (found on cardiac myocytes, hippocampal neurons, renal epithelial cells, and blood platelets) and n-NOS are constitutively expressed and produce low levels of NO through calcium-dependent pathways (92,93), whereas i-NOS is induced

robustly in a calcium independent manner and has been traditionally assigned the role of causing the vascular responses seen in anaphylaxis. Newer discoveries have recognized the constant expression of e-NOS and variable expression of n-NOS on mast cells (94), suggesting that e-NOS (and not iNOS) is the primary vasodilator working potentially through PI_3 and Akt kinases (95).

IL-33 has been associated with iNOS in allergic rhinitis. Anti-IL33 treatment in a murine study led to significant reduction in ovalbumin-specific IgE and cytokine production in mice sensitized and challenged with ovalbumin. Additionally, microarray analysis revealed decreased expression of the NOS2 gene (96).

iNOS is expressed in asthmatic lungs and has been shown to be increased in the sputum of asthmatics compared to healthy controls. iNOS gene deletion resulted in decreased mucus hypersecretion, eosinophilia, and Th2 cytokine generation. Furthermore, polymorphisms in the iNOS gene have been associated with asthma susceptibility (97). Inhibition of iNOS has thus been an attractive therapeutic target, but selective inhibition of iNOS in human asthmatics did not reduce airway hyperresponsiveness after allergen challenge (98). Interestingly, poly(ADP-ribose) polymerase 1 (PARP-) is thought to be necessary for iNOS expression, and inhibition of PARP-1 has been shown to decrease airway hyperresponsiveness after allergen challenge (99). Further work is needed to determine whether iNOS and PARP-1 inhibition are viable strategies in the treatment of asthma.

Clinically, measurement of fractional exhaled nitric oxide (FeNO) is often used to guide management in asthmatic patients. FeNO has been associated with airway eosinophilia and airway inflammation. Prior work with asthmatics with varying severity classifications (mild, moderate, or severe) demonstrated differential iNOS protein/mRNA expression, with highest expression seen in severe asthmatics. Additionally, iNOS protein/mRNA expression correlated strongly with FeNO. Recent studies involving allergen challenges in asthmatics have proposed that iNOS plays a mechanistic role in increasing FeNO levels (100).

Oxidative Products of Arachidonic Acid

Arachidonic acid is a C20:4 fatty acid component of mast cell membrane phospholipids, from which it may be liberated by the action of phospholipase A_2 or by the concerted action of phospholipase C and diacylglycerol lipase. At least 20 potential end products may be generated from arachidonic acid by the two

major enzymes, 5-lipoxygenase and cyclooxygenase, which regulate its fate.

Cyclooxygenase Products

PGD_2 is the predominant cyclooxygenase product generated by human mast cells, whereas human basophils do not generate this molecule. The production of PGD_2 from PGH_2 is glutathione dependent and is blocked by nonsteroidal anti-inflammatory drugs and dapsone. It is a potent vasoactive and smooth muscle reactive compound that causes vasodilation when injected into human skin, induces gut and pulmonary muscle contraction, and, *in vitro*, inhibits platelet aggregation (101). PGD_2 is thought to be responsible for flushing and hypotension in some patients with mastocytosis and to be an important mediator of allergic asthma (102). PGD_2 is further metabolized to PGJ_2, a natural ligand for peroxisome proliferators-activated receptor-γ (103), a nuclear receptor important in diabetes and atherosclerosis, and, possibly, in the inflammatory response.

Immediate IgE antigen-activated PGD_2 production depends on the constitutive expression of cyclooxygenase 1. Later and more prolonged PGD_2 synthesis occurs after antigen challenge of sensitized cells that are stimulated with SCF and IL-10 (104). As aforementioned, PGD_2 can bind to the CRTH2 receptor found on ILC2s and lead to ILC2 chemotaxis, activation, and proliferation. When activated via PGD_2, ILC2s produce the type 2 cytokine IL-13, which has been shown to promote airway hyperresponsiveness, mucus secretion by goblet cells, IgE synthesis, and eosinophil recruitment. IL-13 is the target of the biologic asthma agent lebrikizumab that was shown in a double-blind, placebo-controlled study to improve FEV_1 in the treatment group (32,105). Notably, IL-13 produced by ILC2s can play an immunomodulatory role and dampen mast cell Th2 inflammatory responses by decreasing the synthesis of TNF-α and IL-6 (106). Studies have also shown that the bronchoalveolar fluid (BAL) in severe asthmatics contains higher amounts of PGD_2 compared to mild asthmatics and may be due to higher concentrations of the MC_{TC} subtype in severe asthma (107).

PDG_2 has also been studied in CRS with nasal polyps, aspirin-exacerbated respiratory disease (AERD) and atopic dermatitis. ILC2s with the PDG_2 receptor CRTH2 have been identified in these diseases, and PGD_2 has been theorized to be a key player in AERD and atopic dermatitis pathology. Urinary PGD_2

metabolite was found to be elevated in patients with AERD compared to controls, and was also found to be increased to a greater extent during aspirin reactions. Additionally, nasal polyp TSLP mRNA expression correlated with nasal polyp PGD_2 synthase expression, and TSLP was found to induce the production of PGD_2 in human mast cells (108,109). These studies demonstrate the involvement of PGD_2 in the pathogenesis of type 2 inflammatory responses in AERD.

Lipoxygenase Products

Human mast cells generate 5-lipoxygenase products of arachidonic acid, starting with an unstable intermediate, 5-HPETE (which may be reduced to the monohydroxy fatty acid 5-HETE) or, through leukotrienes synthetase, LTC_4 by addition of glutathione through the action of LTC_4 synthase (LTC_4S). This enzyme and its activating factor termed 5-5-lipoxygenase-activing protein, resides on the outer surface of the nuclear membrane. The initial product of this pathway is LTC_4, from which LTD_4 may be generated by the removal of the terminal glutamine, and LTE_4 by the further removal of glycine. LTC_4, LTD_4, and LTE_4 collectively are termed the cysteinyl leukotrienes and are increased in CRS and asthma (110). A polymorphism in the LTC_4S gene is thought to alter the amount of this mediator generated during biologic reactions (111). The newly discovered crystal structure of LTC_4S demonstrates that the glutathione residue resides in a U-shaped conformation within an interface of adjacent monomers from a trimer formed by four transmembrane α-helices providing a unique binding site for the precursor molecule LTA_4 (112).

The biologic activity of the sulfidopeptide leukotrienes occurs by its binding to two specific G-protein-coupled receptors termed Cys LTR_I and LTR_{II} (113,114). Cys LTR_1 binds LTD_4 with higher affinity than LTC_4 and Cys LTR_2 binds both LTC_4 and LTD_4 with similar affinity. Notably, Cys LTR_1 and Cys LTR_2 do not bind LTE_4 with significant affinity (115). Both receptors are also present on both innate and adaptive immune cells and have been implicated in the development of microvascular leakage with suspected heterogeneous distribution in the microvascular of different tissues (116). In particular, murine studies indicate that CysLT's from mast cells and monocytes/macrophages preferentially utilize $CysLTR_I$ (117) while transgenic animal model of human Cys LTR_{II} suggests $CysLTR_{II}$ has a contributory role in the vascular changes seen in models of passive cutaneous anaphylaxis (118). Recently evidence has

been presented suggesting the presence of a third receptor for cysteinyl leukotrienes, specifically for LTE_4. It is known that LTE_4 utilizes platelets and their receptor $P2Y_{12}$ for eosinophil recruitment to the respiratory tract and the identification of a specific receptor complex involving $P2Y_{12}$ may allow for the development of thienopyridine ($P2Y_{12}$ inhibitor) based treatment for asthma and AERD (119).

Degradation of leukotrienes is rapid and is accomplished by various oxygen metabolites. Clinically useful inhibitors of 5-lipoxygenase or the Cys LTR_I receptors are available and demonstrate efficacy in clinical asthma (120). No clinically available inhibitor of Cys LTR_{II} or for the putative Cys LTR_{III} has been assessed *in vivo*, and the contribution of these receptors to the physiologic manifestations of LTC_4, LTD_4, or LTE_4 in human disease remains speculative.

Leukotrienes are potent and possess a broad spectrum of biologic activity (121). They induce wheal-and-flare responses that are long lived and are accompanied historically by endothelial activation and dermal edema. In the airway, they enhance mucus production and cause bronchoconstriction, especially by affecting peripheral units. Experimentally, there is a decreased presence of TH2-dependent pulmonary inflammation (eosinophil and goblet cell count, amount of mucus and degree of mast cell infiltration) after antigen challenge in murine models lacking LTC_4S (122). In humans, LTD_4 is most active, LTC_4 is intermediate, and LTE_4 is the least potent. LTE_4 has been implicated as an inducer of nonspecific bronchial hyperreactivity. It has been suggested the LTD_4 augments airway remodeling (123), possibly by stimulating matrix metalloproteinase release or activity. All depress cardiac muscle performance and diminish coronary flow rates. Suggestions have also been made that they all also contribute to venoconstriction in the liver during anaphylaxis (124). LTC_4 and LTD_4 have been recovered from nasal washings and bronchial lavage fluids of patients with allergic rhinitis or asthma, whereas LTE_4 has been recovered from the urine. Urinary LTE_4 is increased at baseline in AERD patients compared to asthmatics without aspirin sensitivity (119).

More recently, the development of 5-oxo-ETE through the alternative pathway for 5-HPETE metabolism has been delineated. 5-HPETE gives rise to 5-HETE through peroxidases and subsequently to 5-oxo-ETEs (eicosatetraenoic acids) by 5-hydroxyeicosanoid dehydrogenase (5-HEDH). 5-Oxo-ETE is an extremely potent eosinophil chemoattractant which supercedes PAF in this manner. It is also involved in eosinophilic intracellular calcium mobilization,

actin polymerization, neutrophilic chemotaxis, and at high levels (*in vitro)* airway smooth muscle contraction (125).

LTB_4 is the alternative product of LTA_4 via LTA_4 hydrolase, primarily formed in neutrophils and monocytes. Is a chemotactic agent of many cells, including neutrophils and eosinophils, is implicated in the trafficking of $CD4^+$ and $CD8^+$ cells into the airway upon antigen challenge (126) and theorized to contribute to the late phase of anaphylaxis and to protracted reactions (43).

Phospholipase

Phospholipases are enzymes that convert phospholipids into fatty acids and lipophilic substances. There are four major classes (A–D) that catalyze different reactions in phospholipase breakdown, some of which have been implicated in mechanisms of mast cell and basophil reactions in anaphylaxis. Cytosolic phospholipase A_2 has direct effects in producing arachidonic acid from phospholipid membranes leading to the formation of prostaglandins and leukotrienes. Exogenous phospholipase A_2 (honeybee venom secretory phospholipase A_2) can directly activate human basophils *in vivo* to induce leukotriene production (127). Low-molecular weight secreted phospholipases A_2 ($sPLA_2$s) have been detected in the BAL fluid in both healthy individuals and asthmatics, and are increased during allergen challenge. Lung mast cells express $sPLA_2$ mRNA and have been thought to be the source of $sPLA_2$ in asthma (128). Phospholipase C has many different isoforms one of which, Phospholipase $C\gamma_2$ ($PLC\gamma_2$), has been suggested to be expressed in mast cells and monocytes/macrophages and to play a role in increasing intracellular calcium levels following $Fc\varepsilon RI$ cross-linking of mast cells (129). As aforementioned the phospholipase $C\gamma$ pathway has been thought to be activated during mast cell activation mediated via the MRGPRX2 receptor in humans (47). Phospholipase D (PLD) has two isoforms, PDL_1 and PLD_2, which are actively involved in the signaling process of mast cells (130) but their exact function and mechanisms are still unclear. PLD can be activated (131) and cultured in mast cells (132) and, interfering with the presence of substrates for PLD, has led to suppression of mast cell degranulation (130).

Adenosine

The nucleoside adenosine generated from the breakdown of ATP is released from mast cells on IgE-mediated activation (133). In humans, circulating blood

levels of adenosine are 0.3 µg/mL and are increased after hypoxia or antigen-induced bronchospasm. Adenosine is a potent vasodilator, inhibits platelet aggregation, and causes bronchospasm on inhalation by asthmatics. Adenosine, acting through a cell surface receptor, probably the A2b and A3 subtypes (134,135) enhances mast cell mediator release *in vitro* and potentiates antigen-induced local wheal-and-flare responses *in vivo*. Interestingly the A2 adenosine receptor (A2aAR) has been shown to inhibit IgE-mediated mast cell degranulation while A3 adenosine receptor (A3AR) can potentiate mast cell degranulation. Recent research has proposed that intracellular adenosine can inhibit IgE-mediated mast cell degranulation via intracellular mechanisms involving the equilibrative nucleoside transporter 1 (ENT1) rather than via cell surface adenosine receptors (136). Adenosine binding to its receptor is inhibited by methylxanthines.

Osteopontin

Osteopontin (OPN) is an extracellular matrix glycoprotein involved in bone metabolism but is also found in many cell types in the immune system and is being linked with multiple inflammatory and immune processes, including wound healing, dystrophic calcification, coronary atherosclerosis, tumor cell metastasis, and with the pathogenesis of diseases such as multiple sclerosis and rheumatoid arthritis (137–140). Recent discoveries have elucidated mast cell secretion of biologically active OPN and have suggested it has a role in augmenting mast cell degranulation by FcεRI aggregation and promoting mast cell migration (141). OPN has been found in the asthmatic lung, and the secreted form has been implicated to have an opposing role in the development and containment of Th2 responses through plasmacytoid dendritic cells (142). School-aged children with asthma were found to have significantly higher serum OPN levels than controls (143). Serum OPN levels have been found to be higher at baseline in children with sustained responses after 1 year of venom immunotherapy and could potentially serve as a biomarker for immune tolerance after immunotherapy (144). In patients with allergic rhinitis, blood eosinophilia and asthma were associated with increased serum OPN levels (145). Future studies are needed to further decipher its exact role in the allergic response.

Chemotactic Mediators

Several chemotactic molecules have been characterized by activities generated during IgE-dependent allergic responses. Most remain incompletely characterized. Chemokines, a family of cytokines, have chemoattractant activity

for leukocytes and fibroblasts (Table 3.3). In the C-X-C or α chemokines, the cysteines are separated by one amino acid, whereas the cysteines are adjacent in the C-C or β chemokines. Most α chemokines attract neutrophils, whereas β chemokines attract T cells and monocytes (some also attract basophils and eosinophils). The C-X-C chemokines that attract neutrophils include GRO-α, GRO-β, IL-8, NAP-2, and PF-4. The C-C chemokines that attract eosinophils include eotaxin, MIP-1α, MCP-2, MCP-3, and RANTES. IL-8, MIP-1α, and RANTES are also cell chemoattractants for both mast cells and basophils.

Neutrophil Chemotactic Factors

HMW factors are the most prominent neutrophil-directed activities noted. HMW-NCF (neutrophil chemotactic factor) is released into the circulation soon after mast cell activation (146). Its release in asthmatic patients is antigen dose dependent, inhibited by cromolyn, and accompanied by transient leukocytosis.

LTB_4 and PAF are potent chemotactic agents capable of inducing neutrophil exudation into human skin, and also inducing the production of oxygen radical and lipid mediators. Histamine also alters neutrophil chemotactic responses.

Eosinophil Chemotactic Factors

Historically, PAF was thought to be the most potent and selective eosinophil-directed agent (87) which induced skin or bronchial eosinophilia. More recently, 5-oxo-ETE has been found to be up to 30 times more potent in eosinophilic chemotaxis than LTB_4 or any CysLTs and nearly three times more potent than PAF (125). Other less active eosinophil-directed mast cell products include the tetrapeptides Val or ala-gly-ser-glu (eosinophil chemotactic factor of anaphylaxis [ECF-A]) (147) and others, having a molecular weight of 1,000 to 3,000. The latter have been found in the blood of humans after induction of physical urticaria or allergic asthma. ECF-A is capable of inducing PAF production by eosinophils (148).

Mediators with Enzymatic Properties

Tryptase is the major protein found in human mast cells, and its expression by peripheral blood cells is predominantly by the mast cell with <1% of its expression from the basophil (149). Although it was previously questioned, basophil cells secreting mast cell tryptase have been characterized as their own entity, disputing previously reported hybrid lineages or mast cell lineages as the source (150). Tryptase is a neutral serine protease which is stored in secretory

granules as an active tetramer with a molecular weight of 134 kD (151). There are two tryptase genes α and β. α-Protryptase is secreted constitutively from mast cells as an inactive proenzyme and is the major form of tryptase found in the circulation of normal subjects. β-Tryptase is stored in the secretory granules of mast cells, and its activation involves two proteolytic steps. The first is an autocatalytic intermolecular cleavage of the molecule at an acidic pH and in the presence of heparin or dextran sulfate. The second involves the removal of the remaining precursor dipeptide by dipeptidyl peptidase I (152,153). Tryptase constitutes nearly 25% of mast call granular protein and is released during IgE-dependent reactions. It is capable of cleaving kininogen to yield bradykinin, diminish clotting activity, and generate and degrade complement components, such as C3a and a variety of other peptides. The proteolytic activities of tryptase work best in low pH environments, and β-tryptase is often released into acidic tissues, such as areas of inflammation and poor vascularity (151). Although the exact mechanism for its regulation is not known, β-tryptase can be slowly and incompletely dissociated from heparin proteoglycan by basic proteins, such as antithrombin III (153). Tryptase is not inhibited by plasma antiproteases, and, thus, its activity may be persistent. β-Tryptase released during mast cell degranulation has been suggested to cleave IgE, possibly acting as a natural mechanism for controlling allergic inflammation (154).

The ratio of α and β subtype assays has become useful markers in discerning between systemic mastocytosis and anaphylaxis in which α-tryptase is primarily released in the former and β-tryptase in the later. A ratio of total tryptase (α-protryptase + β-tryptase) to mature (total β-tryptase) of less than 10 suggests the diagnosis of anaphylaxis, whereas systemic mastocytosis is suggested if this ratio is greater than 20 (155).

A chymotryptic protease, termed *chymase*, is present in a subclass of human mast cells, particularly those in the skin and on serosal surfaces, and has thus been used as a marker to identify MC_{TC}. It cleaves angiotensinogen to yield angiotensin, activates IL-1, and is a mucus secretagogue. Other enzymes found in mast cells include carboxypeptidase, which coverts angiotensin I to angiotensin II and cleaves bradykinin and substance P (37); and acid hydrolases.

Structural Proteoglycans

The structural proteoglycans include heparin, various chondroitin sulfates, and cytokines.

Heparin

Heparin is a highly sulfated proteoglycan that is contained in amounts of 5 pg/10^6 cells in human mast cell granules (156) and is released on immunologic activation. Human heparin is an anticoagulant proteoglycans and a complement inhibitor, and it modulates tryptase activity. Human heparin may also be important in angiogenesis by binding angiogenic growth factors and preventing their degradation, and it is essential for the proper packaging of proteases and histamine within the mast cell granule.

Chondroitin Sulfates

Human basophils contain about 3 to 4 pg of chondroitin 4 and 6 sulfates, which lack anticoagulant activity and bind less histamine than heparin. Human lung mast cells contain highly sulfated proteoglycans, chondroitin sulfates D and E, which accounts for the different staining characteristics of these mast cells. Chondroitin sulfate, along with heparin proteoglycans, helps to stabilize and regulate the secretion of granular proteases (157). Mouse models have suggested focal adhesion kinase, a nonreceptor protein kinase, increases the chondroitin/dermatan sulfate content of maturing mast cell granules ensuring an intact microvillous cell surface (158). Exogenous chondroitin sulfate has been studied and suggested to play a role in decreasing Th2 responses (by decreasing IgE, histamine, and Th2 cytokine profile) in animal models (159), but results are limited and mechanisms have not been elucidated.

Cytokines

Although cytokines traditionally have been viewed as products of monocytes-macrophages or lymphocytes, it has been well established that mast cells (160–163) generate many, including TNF-α, IL-1, IL-1ra, IL-3, IL-4, IL-5, IL-6, IL-9, IL-13, IL-16, and GM-CSF (160–163). These molecules may be central to local regulation of mast cell growth and differentiation and may also provide new functions for mast cells in health and disease. Basophils are also a prominent source of IL-4 and IL-13 (160). These cytokines are categorized as those that cause inflammation (IL-1, IL-6, and TNF-α), enhance IgE synthesis (IL-4 and IL-13), stimulate eosinophil growth, survival, localization, and activation (IL-3, IL-5, and GM-CSF); participate in airway remodeling (IL-9) and decrease inflammation (IL-1ra) (160–163). ILC2s are activated by IL-25, IL-33, and TSLP and produce IL-4, IL-5, IL-6, IL-9, and IL-13 (32).

In the murine model, IL-4 and IL-13, through Stat-6-dependent signaling, are implicated in increasing sensitivity to vasoactive mediators by increasing vascular leak (164). The IL-4α receptor on CD4$^+$ T cells appears to be an

important mediator of the anaphylaxis cascade while interferon-γ may be protective (165).

MEDIATOR INTERACTIONS

The mediators generated and released after mast cell activation have been isolated, identified, and characterized as individual factors, whereas physiologic and pathologic events reflect their combined interactions. Given the number of mediators, the knowledge that may have yet to be purified (or even identified), and the lack of understanding of appropriate ratios of mediators generated or released *in vivo,* it is not surprising that there are no reliable data regarding these interactions in health or disease. The number and type of mast cell mediator interactions are potentially enormous, and their pathobiologic consequences are relevant to a variety of homeostatic and disease processes. The best clues to the interaction of mediators are the known physiologic and pathologic manifestations of allergic diseases. It is hoped that the valuable tool of gene knockouts in mice will elucidate critical individual and interactive roles of these molecules.

THE ROLE OF THE MAST CELL AND ITS MEDIATORS IN TISSUE

The most compelling evidence for the role of mast cells and mediators in human tissue is derived from experiments in which IgE-dependent mast cell activation in skin is caused by specific antigen (or antibody to IgE). The participation of other immunoglobulin classes and immunologically activated cells, and thus of other inflammatory pathways, is excluded in such studies by using purified IgE to sensitize nonimmune individuals passively. Activation of cutaneous mast cells by antigen results initially in a pruritic wheal-and-flare reaction that begins in minutes and persists for 1 to 2 hours, followed in 6 to 12 hours by a large, poorly demarcated, erythematous, tender, and indurated lesion (166). Histologic analysis of the initial response shows mast cell degranulation, dermal edema, and endothelial cell activation. The late reaction is characterized by edema; by infiltration of the dermis by neutrophils, eosinophils, basophils, lymphocytes, and mononuclear leukocytes; and, in some instances, by hemorrhage, blood vessel wall damage, and fibrin deposition of sufficient severity to warrant the diagnosis of vasculitis. Similar studies of lung tissue responses, employing passive sensitization, or mast cell–deficient subjects, have only been possible in mice. In humans, a similar dual-phase reaction is experienced by allergic patients who inhale antigen, but the participation of immunoglobulins other than IgE and

of activating cells, other than mast cells cannot be excluded, therefore complicating assessment and preventing unambiguous assignment of any response to a particular immunologic pathway. Such challenges result in an immediate bronchospastic response followed by recovery, and, 6 to 24 hours later, by a recrudescence of asthmatic signs and symptoms (167). The mediators responsible for these pathophysiologic manifestations have not been delineated fully, but clues to their identity can be derived from knowledge of the effects of pharmacologic manipulation, by the identification of mediators in blood or tissue fluid obtained when the inflammatory response occurs, and by the known effects of isolated mediators.

Pharmacologic intervention suggests that the initial phase is mast cell dependent in both skin and lung tissues. The initial response in skin may be inhibited by antihistamines, and in the lungs by cromolyn, aspirin, or antihistamines. In both tissues, corticosteroids effectively inhibit only the late response, reflecting its inflammatory nature. Histamine, TNF-α, tryptase, LTD_4, PGD_2, IL-5, and both neutrophil and eosinophil chemotactic activity are found soon after challenge. The late response is associated with leukocyte infiltration and cytokine release, but not with a unique profile of released mediators. The exact genesis of the early and late reactions is speculative. The concerted action of the spasmogenic mediators, histamine, adenosine, PGD_2, leukotrienes, and PAF seems sufficient to account for all of the immediate pathophysiologic (anaphylactic) responses to antigen. This concept is supported by the knowledge that the early response occurs before a significant influx of circulating leukocytes.

However, mast cell mediators or mediators from antigen-reactive T lymphocytes, epithelial cells, or macrophages may induce such changes, either directly or indirectly. In response to mediators, vascular endothelium, fibroblast, and a variety of connective tissue and epithelial cells then could generate other inflammatory and vasoactive mediators. The late phases in lung and skin tissue are likely to represent the residue of the early response as well as the contribution of active enzymes, newly arrived plasma inflammatory cascades, various cytokines (particularly those inducing endothelial expression of adhesion molecules) (161), and the influx of activated circulating leukocytes. Of direct relevance to leukocyte recruitment are GM-CSF, IL-3, and especially IL-5, which promote eosinophil growth, differentiation, migration, adherence, and activation (168). The late inflammatory response is relevant to the progression of asthma in that patients experiencing the late responses have exacerbation of their

nonspecific bronchial hyperreactivity, whereas this phenomenon does not occur after isolated early responses.

■ HOMEOSTATIC ROLE OF MAST CELLS

Mast cell mediators are likely important in maintaining normal tissue function and participate in the expression of innate immunity. Because mast cells are positioned near small blood vessels and at the host–environment interface, and are thus at crucial sites for regulating local nutrient delivery and for the entry of noxious materials, the potential regulatory role of mediators is obvious. They are likely to be especially important in the regulation of flow through small blood vessels, impulse generation in unmyelinated nerves, and smooth muscle and bone structural integrity and function. The ability to recruit and activate plasma proteins and cells may also activate plasma proteins, and cells may also provide preimmune defense against host invasion by infectious agents. Such a role is most apparent in parasitic infestation but is also likely in the case of other insults. Moreover, the recognition of mast cell heterogeneity implies that differences in mast cells relate to locally important biologic requirements.

Although the homeostatic and pathophysiologic role of mast cell mediators is understood imprecisely, the broadening understanding of their chemical nature and function provides a useful framework for addressing their role in health and disease.

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Evaluation and Management of Immune Deficiency in Allergy Practice

MELVIN BERGER

There is considerable overlap between the manifestations of allergy and respiratory infection (i.e., rhinorrhea, sneezing, coughing, wheezing), and allergy may be a predisposing factor in rhinosinusitis, otitis, and other respiratory infections. Therefore, the allergist must frequently evaluate patients with symptoms attributed to recurrent infections and in which the competence of the patient's immune system has been or should be questioned. Because half or more of all patients with primary immune defects have antibody deficiencies (1–3) and most of them have problems with recurrent sinopulmonary infections, this is not an uncommon condition for which allergist-immunologists are consulted. Other complex immune deficiencies may present with symptoms which overlap with common manifestations of atopy, including dermatitis in Wiskott–Aldrich syndrome (WAS) and hyper-IgE syndrome (HIES), and colitis in the immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, chronic granulomatous disease (CGD), and others (1–3). Recent surveys suggest that the prevalence of diagnosed primary immune deficiencies in the United States is at least 1 in 1,200 persons, and many additional cases are undiagnosed (4). The aim of this chapter is to provide a practical approach to the recognition, diagnosis, and management of such patients, not a comprehensive review of immune deficiency disorders or their molecular bases. More than 250 distinct primary immune deficiencies have been identified, which are classified into nine categories (Table 4.1) (3). Readers who wish a more in-depth analysis of immune deficiency disorders should consult recent consensus Practice Parameters of the Joint Council on Allergy, Asthma and Immunology (1), the Diagnostic and Clinical Care Guidelines of the Immune Deficiency Foundation (2), the 2015 Update and Classification of Primary Immune Deficiencies from the International Union of Immunology Societies (3), or comprehensive texts such as those edited by Ochs et al. (5) or Sullivan and Stiehm (6).

TABLE 4.1 INTERNATIONAL UNION OF IMMUNOLOGY SOCIETIES CLASSIFICATION OF PRIMARY IMMUNE DEFICIENCIES

1. Immunodeficiencies affecting cellular and humoral immunity

2. Combined immunodeficiencies with associated or syndromic features

3. Predominantly antibody deficiencies

4. Diseases of immune dysregulation

5. Congenital defects of phagocyte number, function, or both.

6. Defects in intrinsic and innate immunity

7. Autoinflammatory disorders

8. Complement disorders

9. Phenocopies of primary immune deficiencies

Picard C, Al-Herz W, Bousfiha A, et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. *J Clin Immunol*. 2015;35:696–726.

INDICATIONS FOR AN IMMUNOLOGIC WORKUP

Although many immune-deficient patients have a clear history of distinct episodes of severe infection, allergists frequently see patients with less severe, nonspecific symptoms, such as nasal stuffiness, chronic and recurrent rhinorrhea, or cough, which may be due to infection, allergy, or other factors. The first step in sorting out such complaints is to try to distinguish whether the symptoms are, in fact, due to infection. Inciting factors, such as seasonality, and clearly identifiable triggers may suggest allergic etiologies, but changes in the weather and in seasons are frequently accompanied by changes in exposure to infectious

diseases, especially among school-aged children.

A history of exposure to others with similar symptoms and details such as the presence or absence of fever, description of excessive secretions (clear and watery versus thick and purulent), and the response to antibiotics may help distinguish between infectious and noninfectious etiologies. After an estimate of the real incidence of infection is obtained, this can be compared with benchmarks, such as the "10 Warning Signs of Immune Deficiency" (Fig. 4.1). The incidence of infection should be compared with the incidence for that age group in the community, but the exposure history should also be considered. For example, a 40-year-old who lives alone and works at a computer would be expected to have a different degree of exposure to infectious agents than a kindergarten teacher, day care worker, or pediatric office nurse. College students moving from home to the dormitory for the first time and military recruits often have sharp increases in exposure to infectious disease. Similarly, a first-born baby at home often has a very different degree of exposure to than a similar-aged infant in day care or with many siblings. Generally, the frequency of infection among school-aged children in the United States is about six to eight upper respiratory and/or gastrointestinal infections per year, but as many as one a month while school is in session is not unusual. About half of these may be primary bacterial infections or secondary bacterial sequelae, such as otitis media, rhinosinusitis, pneumonia, or bronchitis.

■ FIGURE 4.1 Ten warning signs of primary immune deficiency. (Presented as a public service by The Jeffrey Modell Foundation and The Centers for Disease Control and Prevention. Developed by The Jeffrey Modell Foundation Medical Advisory Board.)

Patients with clear histories of more than 10 distinct episodes of infection per year, more than 2 documented episodes of pneumonia, or more than 1 life-

threatening infection should be evaluated for possible immune deficiency or other underlying abnormalities. However, the specialist must be careful in interpreting the history from the patient or parent. Frequently, antibiotics are given when the patient does not actually have a bacterial infection, then a failure to respond leads to the conclusion that "antibiotics do not work." This may, in turn, lead to the suggestion that there is something "wrong" with the patient's immune system. Frequent upper respiratory symptoms may represent individual viral infections. On the other hand, respiratory virus infections may be prolonged in immune-deficient patients (7), although there may be chronic infections such as sinusitis that have not been adequately treated despite multiple short courses of oral antibiotics. Patients who present with the complaint of "constant colds" may actually have allergic rhinitis. Densities on chest radiograph may represent atelectasis due to asthma rather than true infiltrates, and should not necessarily be taken as indicating recurrent pneumonia unless there is documentation of concomitant fever, elevated white blood cell count, or positive sputum Gram stain or culture.

Patients with unusually severe infections requiring parenteral antibiotics, prolonged or multiple courses of antibiotics for a single infection, or surgical intervention such as incision and drainage of abscesses or removal of seriously infected tissue (e.g., a segment of lung or infected bone), should probably also undergo screening (see later) to exclude immune deficiency. Patients with unusual or opportunistic infections, or with unusual responses, such as prostration or excessive fever to seemingly common organisms, should also be evaluated for immune deficiency.

Although many patients with primary immune deficiencies present with recurrent and chronic respiratory infections (1,2,8–10), gastrointestinal disorders are also common in these patients (11–14). The combination of recurrent respiratory infections with recurrent gastrointestinal symptoms may prompt immunologic screening even when the involvement of either organ system itself is not severe. Infection with *Giardia lamblia* (15) and bacterial overgrowth in the small intestine are common in patients with antibody deficiencies. These problems may present with cramps or diarrhea after eating, leading to suspicion of food allergy or protein-sensitive enteropathy despite the absence of other manifestations of immunoglobulin E (IgE)- or eosinophil-mediated reactions. Some immune-deficient patients may have organized lymphonodular hyperplasia in the intestine or infiltration of the submucosa with scattered aggregates of lymphocytes (11–13). Patients with gastrointestinal workups or biopsy results not typical for recognized patterns of inflammatory bowel disease should also be

evaluated for immune deficiencies (13).

The presence of nonimmunologic findings on physical examination may also provide indications for evaluation to exclude immune deficiency (Table 4.2). Failure to thrive and/or leveling out of the growth curve in children, and unexplained weight loss in adults, may indicate malabsorption due to intestinal infection or cumulative morbidity of other infections. The importance of recording accurate measurements of weight and height in children at every visit cannot be overemphasized. Severe eczema may suggest HIES, WAS, or IPEX (16–22) although associated pulmonary and skeletal abnormalities may distinguish HIES (18), thrombocytopenia would suggest WAS (22), and colitis would be found in IPEX (19–21). Facial, cardiac, or skeletal features are often suggestive of a recognizable pattern of malformation, such as that seen in DiGeorge syndrome, short-limbed dwarfism, or cartilage-hair hypoplasia (23,24). Characteristic abnormalities of dentition have been described in NF-κB essential modulator deficiency and HIES (25,26). Some forms of HIES are also accompanied by facial and skeletal abnormalities (25–27). Rib flaring and prominent costochondral junctions may be present in severe combined immune deficiency (SCID) due to adenosine deaminase (ADA) deficiency (28). Alopecia and/or endocrinopathies occur with increased frequency in chronic mucocutaneous candidiasis due to mutations in the AIRE gene (29) and in IPEX (18–20). Nystagmus, clumsiness, and other neurologic abnormalities may occur before observable telangiectasias and may suggest ataxia-telangiectasia (30). Neurologic disorders are also common in purine nucleoside phosphorylase deficiency (31). Although delayed separation of the umbilical cord stump is widely considered an indicator of leukocyte adherence protein deficiency, in fact, there is a wide variation in the time at which the stump separates, and this should not be overemphasized in an otherwise well infant (32). Of course, patients with positive newborn screening tests for SCID (see later) or who test positive for human immunodeficiency virus (HIV) should have a complete immunologic evaluation.

TABLE 4.2 PHYSICAL FINDINGS NOT DUE TO INFECTIOUS DISEASE ASSOCIATED WITH SELECTED IMMUNE DEFICIENCY SYNDROMES

I. Facial and Dental Abnormalities

Broad nasal bridge, increased interalar distance	Hyper-IgE syndrome

Hypognathism; low, cupped ears	DiGeorge syndrome
Peg teeth	NEMO deficiency
Failure to lose primary teeth	Hyper-IgE syndrome

II. Other Skeletal Abnormalities

Metaphyseal chrondrodysplasia (short-limbed dwarfism)	Cartilage-hair hypoplasia
Cupped (dysplastic) costochondral junctions, abnormalities of apophyses of iliac bones and vertebrae	Adenosine deaminase deficiency
Multiple fractures	Hyper-IgE syndrome

III. Cardiac Defects

Conotruncal (great vessel) defects	DiGeorge syndrome
Single chamber, anomalous pulmonary veins	Asplenia

IV. Thymic Abnormalities

Hypoplasia or aplasia	DiGeorge syndrome
	Severe combined immune deficiency
Thymoma	Hypogammaglobulinemia (Good syndrome)

V. Central Nervous System Abnormalities

Spasticity, developmental delay	Purine nucleoside phosphorylase deficiency
Ataxia (cerebellar), nystagmus, developmental delay	Ataxia-telangiectasia
VI. Cutaneous Abnormalities	
Eczematoid rashes	Hyper-IgE syndrome, Wiskott–Aldrich syndrome, IPEX
Fine, sparse hair	Cartilage-hair hypoplasia
Poor wound healing, thin scars	Leukocyte adherence deficiency
Cutaneous and ocular telangiectasias	Ataxia-telangiectasia
Oculocutaneous albinism	Chédiak–Higashi syndrome
Alopecia	APECED (chronic mucocutaneous candidiasis)
VII. Endocrine Defects	
Hypoparathyroidism/hypocalcemia	DiGeorge syndrome
Multiple (autoimmune) endocrinopathies	APECED

APECED, autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy; IgE, immunoglobulin E; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked; NEMO, NF-κB essential modulator.

Many immune deficiencies are clearly hereditary, with well-defined patterns of inheritance and molecular defects (1–3). Family members suspected of having these disorders, perhaps because an older sibling has already been diagnosed, should undergo assessment of their immune status. When available, tests for the specific molecular lesion should be included (see later) so that treatment aimed

at correcting or compensating for the basic defect can be instituted early enough to prevent or minimize end-organ damage. Parental screening for the carrier state and/or prenatal testing is now available for many of these disorders and can be used both in counseling and in ensuring that prompt and appropriate therapy is offered to affected newborns. It is important to realize, however, that a negative family history does not rule out a disease that is usually considered hereditary. For example, analysis of large groups of patients with confirmed mutations in Bruton's tyrosine kinase shows that 60% to 75% of the cases are sporadic, suggesting a new mutation on the X-chromosome in that particular patient (8,33).

DOCUMENTING THE HISTORY OF INFECTION

A major goal in questioning the patient and reviewing the medical records is to develop a clear impression of the types of infections from which the patient has suffered, so that subsequent laboratory tests can be targeted to specifically analyze those components of the immune system whose defects would provide the most likely explanation (1,2,34,35). This will be best served by keeping in mind general patterns of infection that might be caused by defects in specific immunologic defense mechanisms. Thus, infections with encapsulated extracellular bacteria, particularly of the respiratory tract, are suggestive of defects in antibody production (1,2,35), which constitute a majority of all immune deficiencies (1–3). Noninvasive mucosal infections may particularly suggest isolated IgA deficiency (36). Infections with opportunistic pathogens, including protozoans and fungi, and severe or recurrent episodes of chickenpox or herpetic lesions, may suggest problems in cell-mediated immunity (1–3,34). Failure to clear bacteria promptly from the blood stream, resulting in bacteremia/sepsis or hematogenously disseminated infections such as osteomyelitis, may be seen in deficiencies of C3 or early-acting components of the complement system (35,37), but may also indicate asplenia or poor reticuloendothelial system function, as in sickle cell disease. Recurrent or disseminated neisserial infections may suggest deficiency of the complement components that form the membrane attack complex (37). Abscesses and/or infections with unusual bacteria or fungi may suggest neutropenia, defects in neutrophil function, or in interleukin-17 (IL-17) or related signaling pathways (35,38–41). Enteroviral meningoencephalitis may suggest X-linked agammaglobulinemia (33,42). On the other hand, it should be remembered that normal babies have increased susceptibility to infections usually controlled by T cells and γ-interferon (43), so that isolation of some organisms otherwise

considered "opportunistic" should not always be cause for alarm.

The number and types of infections and their individual and cumulative morbidity should be assessed. It is necessary to carefully exclude other causes of nonspecific symptoms; for example, is sniffling or congestion due to allergy or other types of rhinitis? In contrast, documentable rhinosinusitis is a frequent complication of primary immune deficiency (44). A recent study of 239 adults (mean age = 48 ± 11 years) referred for chronic rhinosinusitis reported that 23% of patients failed to develop protective titers to more than seven serotypes in the 23-valent pneumococcal polysaccharide vaccine (45). Interestingly, 71% of these patients also carried the diagnosis of asthma. A meta-analysis of 13 studies which collectively included over 1,400 patients reported that 23% of patients with chronic rhinosinusitis for >1 year not controlled by surgery were deficient in IgA, IgG, or IgM (46). If cough is a major complaint, is it due to sputum production, irritation, or other causes? Could it represent cough-equivalent asthma? If failure to thrive and cough are both present, could the patient have cystic fibrosis? Celiac or other forms of inflammatory bowel disease may mimic hypogammaglobulinemia in children with poor weight gain who also have frequent upper respiratory infections which by themselves would not be considered significant.

Isolation and identification of responsible organisms is clearly the gold standard for rigorous diagnosis of infection. Documentation of fever, white blood count with differential, and sensitive but nonspecific measures such as the erythrocyte sedimentation rate and C-reactive protein can help distinguish between recurrent/chronic sinusitis and headaches due to other causes. These tests can also help for the differential diagnosis of recurrent cough or other chest symptoms. The importance of culture and examination of smears of nasal secretions for bacteria and neutrophils versus eosinophils cannot be overemphasized in distinguishing infectious from allergic and other noninfectious etiologies, particularly in small children. In some cases, the most appropriate step in the workup is to send the patient back to the primary care physician with instructions to have appropriate cultures and the readily available laboratory tests listed above performed every time an infection is suspected or the symptoms recur. Similar steps may also help in identifying adults with recurrent headaches erroneously attributed to chronic/recurrent sinusitis. Sometimes, culture results point to the diagnosis, as in the case of *Pseudomonas aeruginosa* suggesting cystic fibrosis, or invasive aspergillosis suggesting neutropenia or CGD (34,35,40). Chronic or recurrent *Cryptosporidium parvum* infection may suggest the X-linked hyper-IgM syndrome (CD40 ligand

deficiency) (47,48), and, of course, *Streptococcus pneumoniae* or *Haemophilus influenzae* suggest antibody or complement deficiency (1,2,8,35,37,42).

Clues to the severity and overall morbidity of infection may be obtained by asking whether hospitalization or intravenous (IV) antibiotics have been required to treat infections or whether oral antibiotics have generally been sufficient. The response to therapy should be evaluated carefully. Continued high fever or other symptoms suggesting a lack of response of culture-confirmed bacterial infection to antibiotics is more likely indicative of a significant immune deficiency than is the frequently seen pattern in which the fever and symptoms resolve promptly when antibiotic therapy is started (e.g., for otitis media) only to recur again shortly after the prescribed course of therapy is concluded. The latter may actually represent a distinct new infection. This pattern is quite commonly seen in children in day care and in adults with frequent exposure to small children. Similarly, it is also important to distinguish inadequate or inappropriate therapy (i.e., antibiotics for viral upper respiratory infections) from failure to respond, and it is important to differentiate chronic infections from recurrent episodes. Absence from school or work should be quantitated if possible, and any long-term sequelae or disability should be documented. The family history should include questions about siblings and preceding generations. Family trees with premature deaths of male infants should raise suspicion of X-linked immune deficiencies (Table 4.3) although the absence of such a family history does not rule out spontaneous mutations (8,33). Questions should also be asked about the family history of asthma and allergy as well as other genetic diseases that may present with recurrent infection, such as cystic fibrosis. In evaluating a child, it may be important to determine whether the parents have died prematurely or have known risk factors for HIV infection.

TABLE 4.3 MAJOR INHERITED IMMUNE DEFICIENCIES

DISORDER	DEFECTIVE GENE OR LOCUS
I. X-Linked	
Primarily B-Cell Defect or Deficiency	
Bruton's (X-linked) agammaglobulinemia	Bruton's tyrosine kinase (BTK)

X-linked hyper-IgM syndrome	CD40 ligand (gp39, CD154)
Wiskott–Aldrich syndrome	Wiskott–Aldrich syndrome protein (WASP)

Severe Combined Immune Deficiency

X-linked severe combined immune deficiency	Cytokine receptor common chain (γ c chain)

Phagocyte Defects

Chronic granulomatous disease (about 65%)	Gp91 phox component of cytochrome b245
Severe glucose-6-phosphatase deficiency	G-6-PD
Properdin deficiency	Properdin

II. Autosomal Recessive

Primarily B-Cell Defect or Deficiency

Immunoglobulin heavy chain deletion	Indicated gene on chromosome 14
κ-Light chain deletion	22p11
Autosomal agammaglobulinemia	Multiple individual genes
Common variable immune deficiency	Multiple individual genes
Ataxia-telangiectasia	*ATM*, 11q22.3

Hyper-IgM	Activation-induced cytidine deaminase
	Uracil-N-glycosylase (UNG)

Primarily T-Cell Deficiency

DiGeorge syndrome	22q11 microdeletion
Zeta chain–associated protein deficiency (ZAP-70 def)	2q12

Severe Combined Immune Deficiency

Adenosine deaminase deficiency	20q13
Janus kinase 3 (Jak 3) deficiency	19p13
Purine nucleoside phosphorylase deficiency	14q13.1

Natural Killer Cell Defect

NEMO	NF-κB essential modifier

Phagocyte Defects

Chronic granulomatous disease (35%)	Gp47phox or p22phox components of neutrophil oxidase
Leukocyte adherence deficiency type I	CD18 common β chain of leukocyte integrins

Leukocyte adherence deficiency type II	Sialyl-Lewis X (ligand for E-selectin)
Other complement component defects	Various autosomes

IgM, immunoglobulin M.

The age at onset of infections of unusual frequency or severity may yield important insights into immune deficiencies in children. Term newborns have IgG levels equivalent to those of their mothers, because IgG has been transferred across the placenta (49). Thus, babies who have problems with infections during the first few months of life may have T-cell or phagocyte problems but are less likely to have agammaglobulinemia or other isolated problems in antibody production. In contrast, disorders of antibody production are more likely to present after the age of 6 months. The history of exposure must be carefully considered because the frequency of common infections often increases after a child's exposure to infectious agents increases on starting day care or preschool, particularly if there are no siblings in the home. Although patients with severe antibody deficiency such as that seen in Bruton's agammaglobulinemia classically present between 6 months and 2 years of age (8,33,42), that diagnosis as well as the diagnosis of hyper-IgM syndromes are often delayed until later in childhood (8,33,42,47,48). Common variable immunodeficiency (CVID) may present at any age (50–52). That diagnosis is frequently delayed by 8 to 10 years from the onset of a distinct increase in morbidity due to infection. Diagnosis of CVID in older children and young adults may represent an early-onset deficiency that has not been previously recognized or a newly acquired problem. Just as some infants may have delayed development of the full range of immune responses (53), it seems likely that some adults may undergo premature senescence of immune responsiveness (54) and may present with recurrent bacterial infections and/or activation of latent infections (i.e., shingles, tuberculosis) in their 40s or 50s. In addition, antibody deficiency has been increasingly recognized in the fifth to seventh decades of life, or even later (55). Late-onset infections with nontuberculous mycobacteria have been reported in Asian adults with acquired antibodies to γ-interferon (56).

THE PHYSICAL EXAMINATION IN CASES OF SUSPECTED IMMUNE DEFICIENCY

The physical examination often provides important evidence for or against immune deficiency and may also allow the physician to critically assess the

cumulative morbidity due to infection. Most importantly, the presence or absence of lymphoid tissue should be carefully documented. The absence of visible tonsils in patients who have not had them surgically removed and the absence of palpable cervical or inguinal lymph nodes should promote a strong suspicion of a significant antibody deficiency because the bulk of these tissues is composed of B-lymphocytes involved in antibody synthesis. Conversely, the presence of palpable lymph nodes and easily visible tonsils essentially excludes Bruton's agammaglobulinemia and may suggest the absence of SCID, but does not help one way or the other with the diagnosis of CVID or X-linked hyper-IgM syndrome. The presence of cervical or peripheral adenopathy, splenomegaly, or hepatomegaly may suggest CVID, HIV, CGD, or other abnormalities. Many anatomic findings are associated with immune defects in recognizable malformation syndromes (Table 4.3); characteristic rashes may suggest WAS or HIES (16–18); and craniofacial abnormalities with or without cardiac defects may suggest DiGeorge syndrome (57,58). Secondary effects, such as failure to thrive, weight loss, and/or short stature, may suggest significant morbidity due to chronic or recurrent infection. Scars from incision and drainage of abscesses or from drainage or reduction of enlarged lymph nodes may indicate significant morbidity from neutrophil defects.

Autoimmune phenomena (59,60) and rheumatic complaints (61), including infectious or chronic arthritis, are common in patients with CVID and other primary immune deficiencies, and may suggest evaluation for immune deficiency, even if the infection history is not impressive.

Careful assessment of the tympanic membranes, sinuses, and chest is extremely important in evaluating patients suspected of having antibody deficiency syndromes. The quantity and characteristics of secretions should be documented and should be determined whether observed abnormalities are acute or chronic. In this regard, high-resolution (thin-slice) computed tomography (CT) scans of the chest and formal pulmonary function testing may be very helpful (62–65). Bronchiectasis, areas of "ground-glass" density in the lung parenchyma, and/or hilar adenopathy may suggest the presence of subclinical chronic disease, which could be associated with antibody deficiency and/or CVID (62–65). Clubbing of the digits may also provide an important indication of chronic lung disease.

GENERAL LABORATORY SCREENING TESTS

Guidelines for the diagnosis and management of immunodeficiency and handy

algorithms are available from the Joint Council on Allergy, Asthma, and Immunology (1), the Immune Deficiency Foundation (2), and the Jeffrey Modell Foundation (http://www.info4PI.org). These can help prioritize screening tests that might be ordered and interpreted by the primary physician and define situations in which referral to the specialist becomes appropriate. Often, the primary care physician can already have these results in hand when the specialist is called to determine whether referral is appropriate.

A review of laboratory tests already obtained by the primary care physician may yield important clues to the presence of an immunologic disorder and may expedite evaluation of patients by suggesting which specialized tests are most likely to be informative. The complete blood count (CBC) and differential is a critical first step. It is important to remember that lymphocyte counts in newborns should be higher than that in older children and adults and that age-appropriate norms must be used (1,66). Neutropenia may be a primary abnormality, or may accompany X-linked agammaglobulinemia (8,39,42). General blood chemistry panels usually show low total protein but normal albumin in agammaglobulinemia (67). A low uric acid level may be indicative of ADA deficiency or purine nucleoside phosphorylase deficiency (68), whereas low serum calcium may suggest DiGeorge syndrome or autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy.

In addition to assessing the airways and lung parenchyma, the chest radiograph should be reviewed for the absence or presence of a thymus in infants and for the possibility of a thymoma, which may be associated with hypogammaglobulinemia in adults (69). Hyperinflation with patches of atelectasis, suggestive of asthma, might suggest that additional details should be carefully reviewed in patients referred for cough or recurrent pneumonia. The presence of old scars and active disease should be documented. Abnormalities of the ribs resembling rickets can be seen in ADA deficiency (28); abnormalities of the great vessels may suggest asplenia (70) or DiGeorge syndrome (57,58) or may steer the workup away from immune deficiency and toward Kartagener syndrome (situs inversus and ciliary dysmotility) (71).

IMMUNOLOGIC SCREENING TESTS

Tests to screen for immune deficiency can be done in most regional laboratories and community hospitals, with results available in a few days. These should include measurement of the major immunoglobulins and consideration of IgG subclasses. In older adults, serum protein electrophoresis should be included

because patients with monoclonal gammopathy, multiple myeloma, or chronic lymphocytic leukemia (CLL) may have antibody deficiency coexisting with a normal total level of the class of immunoglobulin that includes the paraprotein (M protein). Interpreting serum concentrations of IgG and its subclasses is often less than straightforward (1,2). First of all, age-specific norms must be used, because of the marked changes in values during the first 2 years of life (72). Although some laboratories may report IgG concentrations as low as 200 mg/dL as "normal" in 3- to 6-month-old infants, concentrations of less than 400 mg/dL frequently fail to provide sufficient protection. Second, even within a given age group, most laboratories report a normal range whose upper limit may be two or more times its lower limit. It should be remembered *that the total serum IgG concentration represents the sum of hundreds of separately regulated responses*, rather than a single variable under tight control, like that of an electrolyte or a blood glucose. Concentrations of IgG, and particularly its subclasses, vary not only among individuals of the same age with different exposure histories but also in a single individual at different times. Thus, before any conclusions are reached about the diagnosis of IgG subclass deficiency, the tests should be repeated several weeks apart. Analysis of specific antibody titers should also be considered in pediatric patients and should be performed in adults (see discussion later in this chapter). Especially in babies younger than 1 year of age, the results of any single measurement may be less important than the trend over several months (53,72).

In judging the adequacy of the IgG concentration in a given individual, the history of exposure and the frequency of documented infections must be considered. Thus, normal individuals with frequent exposure to pathogens and those whose host defenses are compromised by conditions that do not affect lymphocyte responses, such as cystic fibrosis and CGD, often have elevated total serum IgG concentrations. This may be considered a physiologic adaptation or the response of a normal immune system to increased or persistent antigen stimulation. IgG concentrations toward the lower limit of normal in patients with comparably increased morbidity but without an underlying nonimmunologic defect may thus actually indicate relative deficiency in specific antibodies and should be evaluated further, as explained in the subsequent sections.

In addition to those conditions in which paraproteins may conceal true antibody deficiencies within normal total IgG levels, nonspecific polyclonal B-cell activation can cause the total IgG and/or IgM level to be within the normal range or even elevated, while specific antibodies may actually be deficient. This is not unusual in systemic lupus erythematosus, Epstein–Barr virus infection, and

HIV infection (73,74). Finding low or absent serum IgA together with low-normal or borderline levels of one or more IgG subclasses, particularly subclass 2, should also raise suspicion of more severe defects in specific antibody production than would be suggested by the total IgG concentration per se, and such patients should also be investigated further (75). Elevated serum IgE and IgA concentrations may be found coexisting with deficiency of antibodies to polysaccharides in WAS, and extremely high IgE levels may suggest, but are not by themselves diagnostic of, HIES.

Quantitation of lymphocyte subtypes by flow cytometry is now widely available and should be included as a screening test in all patients in whom cellular immune deficiency is suspected (76,77). A CBC with differential should always accompany lymphocyte surface marker analysis so that the absolute number of any given type of cell per cubic millimeter of blood can be calculated. As with immunoglobulin determinations, age-specific norms should be used (66). This is extremely important because normal newborns and infants should have higher T-cell counts than older children or adults, and T-lymphopenia suggests SCID (66,76,77). The physician should be careful about which specific test or panel is ordered because, in the era of widespread treatment of HIV, many laboratories offer a standard "lymphocyte surface marker panel," which includes only CD3, CD4, and CD8 cells. Because antibody deficiency due to decreased B-cell number or function is the most common type of primary immune deficiency, natural killer (NK), and B cells should also be quantitated. Analysis of naïve and memory (CD27$^+$, "class-switched" or not) B-cell subsets and surface immunoglobulins is important for the classification and prognosis of CVID (78). In addition, because patients with CLL may present with antibody deficiency, the ratio of lymphocytes expressing κ and λ light chains should also be determined. Analysis of T-cell subsets, B cells, and NK cells frequently provides important clues to the actual molecular defect in many cases of SCID (see later). The exact defect can often be confirmed by analysis of activation markers and intracellular signaling molecules, many of which can now also be analyzed using flow cytometry (76,77). Disorders due to mutations in lymphocyte surface molecules, such as CD40 ligand (CD154) deficiency in X-linked hyper-IgM syndrome and Fas (CD95) deficiency in the autoimmune lymphoproliferative syndrome, are readily diagnosable by flow cytometry, as are several disorders of neutrophil adherence. Defects in the neutrophil microbicidal oxidase pathway (i.e., in CGD) can also be detected by flow cytometry, using dyes such as dihydrorhodamine, which are taken up by the cells but fluoresce only when the cells produce H_2O_2 (76,77).

More rare deficiencies involving other arms of the immune system can also be identified and characterized at this level of testing. In patients suspected of defects in T-cell–mediated immunity, the overall functional activity of T cells is best assessed by determining the patient's ability to mount cutaneous delayed hypersensitivity reactions to recall antigens, such as candida, mumps, or tetanus toxoid (79). Obviously, delayed hypersensitivity skin tests have little meaning in children younger than 2 years of age, who may not be adequately immunized. Patients who have infections suggestive of defects in T-cell–mediated immunity should also undergo HIV screening.

The CBC will give an indication of the number of phagocytes. Assessing their function can often be done by flow cytometry but may require more specialized laboratory capabilities (80,81). Complement screening should include measurement of the serum C3 concentration and the total hemolytic activity (CH_{50}) because the former may be seriously reduced without affecting the latter. The CH_{50} is the best overall screening test for complement defects and is zero in cases of late component defects, such as those that predispose to recurrent or disseminated neisserial infections (37). However, serum for this test must be handled carefully, and repeat testing is often required. In patients with a history of bacteremia, sepsis, or hematogenously spread infection, a careful review of the peripheral blood smear, looking for Howell–Jolly bodies in the erythrocytes, and/or special microscopic examination for pits in their membranes (82), may suggest anatomic or functional asplenia.

DETAILED IMMUNOLOGIC LABORATORY EVALUATION

Although frank hypogammaglobulinemia, neutropenia, and complete deficiency of a component of the classic complement pathway can be detected by the screening laboratory tests described previously, detailed testing is necessary to detect more subtle immune deficiencies. This level of testing is also frequently necessary to characterize severe defects more completely and in complex syndromes involving autoimmune or inflammatory manifestations in addition to infections.

Because of the possibility that clinically significant antibody deficiency may be present even when the total serum concentrations of the major immunoglobulin classes and IgG subclasses are normal, specific antibody production should be assessed whenever the clinical presentation suggests recurrent bacterial infections, particularly of the respiratory tract. This may not

be necessary if the major immunoglobulin classes themselves are absent or severely depressed. Specific antibody titers should be measured against polysaccharide as well as protein antigens (83–86). Although measurement of isohemagglutinins (antibodies to the A, B, or both blood group substances in patients of other blood groups) may be used to screen for the ability to produce antibodies against polysaccharides, the availability of specific antipolysaccharide antibody titers has decreased dependence on those assays.

If specific pathogens have been isolated and identified (e.g., from effusions at the time of insertion of tympanostomy tubes, endoscopic drainage of paranasal sinuses, or expectorated or induced sputum samples), antibodies against those specific organisms could also be measured. In addition, antibodies against common immunizing agents should be measured (86). We usually request measurement of antibodies against tetanus and diphtheria toxins and several pneumococcal polysaccharides as well as *H. influenzae* type B polysaccharide (84–86). Testing for these and additional antibody titers are available in many commercial laboratories and are sometimes referred to as a *humoral immunity panel*.

An advantage of using these particular antigens is that they are contained in readily available, well-tested vaccines, which often have already been given or will be clinically indicated for the patients in question, so that exposure to the antigen is definite (84–86). Obtaining titers before, as well as 4 to 8 weeks after, immunization allows comparison of the response to each antigen. The absence of a threefold rise in titer after immunization and/or failure to achieve protective levels indicates that the patient is unable to mount specific antibody responses (84–86). This may be seen either with protein or polysaccharide antigens and may indicate a failure to recognize or process properly an entire class of antigens. This may occur in what has been termed *specific polysaccharide antibody deficiency*; or the failure to respond to certain particular antigens may be considered a "lacunar" defect. Deficient vaccine responses may also be seen with "normal" Ig levels in patients with polyclonal B-cell activation or lymphoma (see above).

In some rare cases, patients already receiving immunoglobulin infusions may require assessment of their own specific antibody production, which may be difficult because antibodies against many common antigens will have been acquired passively. In this situation, the immunoglobulin therapy can be stopped for a few months (with prophylactic antibiotic coverage, if necessary) so that the patients can be immunized and their own antibody production measured while

they are being reassessed clinically. If this is not possible, special test antigens, such as keyhole limpet hemocyanin and the bacteriophage øX174, can be obtained from specialized centers. Because most individuals and plasma donors have not been exposed to these antigens, commercial immunoglobulin preparations do not contain antibodies against them, and they can be used to assess *de novo* specific antibody formation.

Specific T-cell function is most commonly tested by measuring the incorporation of ^{3}H-thymidine into the newly formed DNA of rapidly proliferating lymphocytes after stimulation *in vitro* (87). Lectins, proteins that bind common polysaccharides on the surface of human cells, are frequently used as the stimuli. Because these proteins stimulate most human lymphocytes, regardless of prior antigen sensitization, they are called *mitogens*, and tests using them are referred to as *lymphocyte mitogen proliferation assays*. Plant-derived lectins typically used for mitogen proliferation assays include concanavalin A, phytohemagglutinin, and pokeweed mitogen. The results of ^{3}H-thymidine incorporation assays may be expressed as radioactivity (counts per minute) in the cells, or as the ratio of incorporation in parallel cultures of mitogen-stimulated versus unstimulated lymphocytes, also referred to as the *stimulation index*. Mitogen stimulation tests are useful even in newborns who have not received any immunizations. These tests may be particularly informative about lymphocyte function and competence in babies with partial T-cell deficiency, such as in DiGeorge syndrome (88). Disadvantages of these tests include the requirements for several milliliters of blood, which may be prohibitive for small newborns; time constraints that may be imposed by the laboratory to facilitate isolation of the mononuclear cells during normal working hours; and the fact that the cells must be cultured for several days (usually 48 to 72 hours) before they are "pulsed" with ^{3}H-thymidine to assess its incorporation.

To surmount these difficulties, many laboratories are now using flow cytometry assays based on the appearance on the lymphocyte plasma membrane of early activation markers such as CD69 (76,77). Mixed lymphocyte cultures, in which a patient's T cells are stimulated by a relative or other potential donor's lymphocytes that have been irradiated to prevent them from proliferating (and vice versa), are also used to test T-cell competence and to determine histocompatibility in cases in which bone marrow transplantation is contemplated. Staphylococcal enterotoxins are also often employed as stimuli in proliferation assays because they are "superantigens" or to antibodies like anti-CD3, which stimulate broad families of T cells by binding to parts of their T-cell receptors other than the antigen-binding site. The response to superantigens is

thus also independent of prior antigen sensitization. T-cell proliferative responses to recall antigens may also be assessed using similar techniques. However, because fewer T cells respond to any given antigen than to the more broadly reacting mitogens (above), these tests commonly involve 4- to 5-day incubation periods before the ^{3}H-thymidine incorporation is determined. The Cowen strain of *Staphylococcus aureus* may be used as a T-cell–independent stimulus for B-cell proliferation.

Obviously, antigen responses can only be expected if the patient has been exposed to the antigen in question. Thus, antigen stimulation tests are usually not useful in early infancy. However, if an older child is known to have received his or her scheduled immunizations, or if candidal infection has been obvious, the response to soluble candida preparations and vaccine antigens such as tetanus toxoid may be useful. In patients with opportunistic infections suggestive of AIDS or positive screening tests for HIV, confirmatory tests, such as Western blot, and quantitation of viral load should be performed. Absolute CD4 number and T-cell function should also be assessed as part of the detailed evaluation (89).

Detailed laboratory analysis in patients suspected of phagocyte disorders should include assessment of neutrophil chemotaxis and the oxidative respiratory burst that accompanies phagocytosis (80,81). Chemotaxis is assessed by measuring the migration of polymorphonuclear leukocytes through agar gels or across filters. The oxidative burst can be assessed by flow cytometry or the nitroblue tetrazolium test, in which a soluble yellow dye is reduced to an easily visible blue intracellular precipitate. If the CH_{50} was abnormal on screening, the actual deficient component can be identified by functional testing in reference laboratories. These laboratories can also screen for abnormalities of the alternative and lectin pathways, which may be indicated in patients who have recurrent bacterial infections or bacteremia and sepsis despite normal results in tests for antibodies and the classic complement pathway.

NEWBORN SCREENING FOR SEVERE COMBINED IMMUNE DEFICIENCY

As of 2016, 42 US states, the District of Columbia, Puerto Rico, and the Navaho Nation include quantitation of T-cell receptor exclusion circles (TRECs) as part of their neonatal screening programs, and 5 more states are planning or set to launch pilot programs (2,90–92). These assays use polymerase chain reactions to quantitate small circular pieces of DNA which are excised during the

rearrangement of antigen receptor genes during the formation of T cells, and thus are really indicative of T-cell lymphopenia and not SCID per se. Therefore, low results on TREC screening tests must be followed up with specialized testing to characterize the molecular diagnosis of SCID, determine another cause for the lymphopenia, or rule out falsely low values (90–92). With the widespread availability of TREC screening, it has become apparent that SCID is more frequent than originally believed, with current estimates closer to 1 in 50,000 live births than 1 in 100,000 (1,90–92). Molecular diagnosis is also necessary for accurate genetic counseling. With early diagnosis, close to 90% of SCID babies can survive due to stem cell transplants (93–95), enzyme replacement (96) or gene therapy (96–98).

If lymphopenia is confirmed, evaluation of lymphocyte subsets should be performed by flow cytometry as quickly as possible because the results should be highly suggestive of the exact molecular lesion and may have important prognostic implications (76,77). In particular, relative preservation of B cells in SCID patients with very low T- and NK-cell counts may suggest deficiency of the important signaling kinase Jak 3 (99,100) or the common cytokine receptor γ chain (100), which is necessary for T-lymphocyte development and is the site of mutations in most cases of X-linked SCID. B, T, and NK cells may be present in equal numbers in forms of autosomal recessive SCID not due to ADA deficiency (76,77). Relatively selective deficiency of CD8 cells is characteristic of deficiency of Zap 70, a protein kinase important in T-cell signaling. The most likely defect can then be confirmed in specialized research laboratories using assays for the specific protein (by Western blot or flow cytometry) or gene that is suspect.

Babies with SCID, their parents, and siblings should promptly undergo human leukocyte antigen typing to evaluate the possibility of hematopoietic stem cell transplantation (HSCT), which is curative in many cases (93–95). This is best accomplished in the first month of life, before there has been end-organ damage and/or chronic infection (92,93). If there is no potential donor who matches at all loci, transplantation of T-cell–depleted marrow from a donor with a mismatch at one or more loci might be considered, but is performed only at certain research centers. There may be mild or delayed presentations of SCID due to enzyme deficiencies, such as purine nucleoside phosphorylase deficiency or ADA deficiency. Making the correct diagnosis as early as possible is especially important in the latter because enzyme replacement with bovine ADA conjugated with polyethylene glycol (Adagen) is commercially available and often ameliorates the immune defect (96). This can serve as a bridge until stem

cell transplantation or gene therapy is performed or as long-term replacement if the patient does not have a suitable donor (96). In T-cell deficiencies with impaired mitogen responses, anticoagulated whole blood should be sent to a research center with expertise in these assays (87). Gene therapy has been used with some success in ADA deficiency and in deficiency of the cytokine receptor γ chain (96–98). Therefore, in cases of apparent SCID in which B cells are present (76,77), early definition of the exact defect is important.

◼ MOLECULAR GENETIC DIAGNOSIS

Advanced testing to pinpoint the molecular lesion in cases of confirmed immune deficiency is usually performed in research laboratories. However, an additional level of definition is now possible in many hospital and commercial laboratories and may provide prognostic and genetic counseling information for patients and their families. Defining the molecular defect is important in the management of immune-deficient patients, because several forms of specific therapy are already available and new modalities are being developed at a rapid rate. Furthermore, when inflammatory and/or autoimmune complications predominate over infections, in cases that would previously have been classified as CVID, definition of the molecular defect may allow selection of the most appropriate inhibitors of abnormally activated signaling pathways rather than overreliance on steroids or nonspecific immunosuppressives (101,102). The pattern of X-chromosome inactivation (103) can be used to determine whether female family members are carriers of Bruton's agammaglobulinemia, WAS, neutrophil defects, and other, but not all, X-linked disorders (33,42,103). Fluorescence in situ hybridization can be used to confirm microdeletions in chromosome 22q11.2 in patients suspected of having DiGeorge or velocardiofacial syndromes, compound anomaly syndromes that may include thymic hypoplasia and partial T-cell deficiencies (57,58).

   Careful delineation of the phenotype and analysis of lymphocyte subsets and activation/signaling pathways by flow cytometry can usually narrow a given patient or family's diagnosis to a subset of known genetic defects which can then be selectively analyzed by high-throughput "next-generation sequencing" (NGS) techniques. Using specialized instrument platforms, such as Illumina, Roche or Ion Torrent sequencers, and commercially available reagent kits (e.g., from Agilent), NGS can often yield a molecular diagnosis within a day or two at a cost of a few thousand dollars or less. NGS involves parallel sequencing of millions of small fragments amplified from the patient's DNA. Advanced, computerized bioinformatics are then used to piece together the larger sequence by mapping

the individual, overlapping fragmentary sequences to the human reference genome. Each stretch of DNA should be sequenced at least 20 times, providing high "depth" (multiple different overlaps repeatedly sequenced) to deliver accurate data (104,105). NGS can be used to sequence whole genomes, including coding and intervening (intron) sequences, narrowed to the coding regions of all of the 22,000 known genes ("whole exome sequencing") or focused on relatively smaller sets of individual genes already implicated in the class of immune deficiencies suspected (104–108). The latter are selected by targeted enrichment and amplification of suspected areas of interest from the whole genome. Thus, although there are 22,000 known human genes, the most recent compilations list approximately 260 distinct molecularly defined immune deficiencies (2,3). Arrays and software for amplifying and simultaneously analyzing 148 known sites of mutations which have been reported to result in antibody deficiencies (107) and 161 mutations which define a broader range of defects (108) have been developed. In the case of previously unknown genetic lesions, many new defects have been discovered through the use of combinations of genome-wide linkage analysis and/or analogy to defects defined in mice together with whole genome or whole exome NGS (104–106).

EARLY MANAGEMENT OF CELLULAR AND SEVERE COMBINED IMMUNE DEFICIENCY

Infants with significant defects in T-cell number or function and those with SCID are not only at great risk for infection with opportunistic pathogens but also may suffer from severe or overwhelming infection with attenuated live viruses used for immunization (92,109). They may present with rashes and eosinophilia due to disregulated oligoclonal autologous T cells or graft-versus-host disease (GVHD) from maternal or transfused leukocytes, as in Omenn syndrome and other severe defects (110,111). Special precautions must be initiated as soon as SCID or a serious combined immune defect is suspected, while the immunologic workup is proceeding and plans for referral and definitive treatment are being formulated. First, any blood products that are given must be *cytomegalovirus* free and irradiated to prevent transfusion of viable lymphocytes that could cause GVHD. Second, live virus vaccines must be avoided (109).

With current recommendations in the United States abandoning the use of the live attenuated oral polio vaccine and replacing it with inactivated vaccine only, polio is less of a risk. However, immunization with Bacille Calmette–Guérin vaccine is practiced in many other countries and may lead to disseminated or

fatal infection. Live measles–mumps–rubella and varicella vaccines should also be avoided. Prophylaxis with varicella-zoster immune globulin should be given if infants with T-cell defects or SCID are exposed to children with chickenpox or adults with zoster. Trimethoprim-sulfamethoxazole or other appropriate regimens should be should be used for prophylaxis against *Pneumocystis jiroveci* (formerly *Pneumocystis carinii)* pneumonia (112), and prolonged courses of nystatin and/or systemic antifungals may be necessary to control candida. The use of passive immunization against respiratory syncytial virus (Synagis) and IV or subcutaneous immune globulin should be considered, particularly in low birthweight infants and in those older than 6 months of age. This may be required for more than a year, even in children who have received HSCT, because functional B-cell engraftment is often delayed and/or incomplete.

MANAGEMENT OF ANTIBODY DEFICIENCY SYNDROMES

Because half or more of all primary immune deficiencies involve defects in antibody production, management of these patients is a common part of allergy-immunology practice. Patients with X-linked agammaglobulinemia, hyper-IgM syndromes, and other severe immunoglobulin deficiencies clearly require immunoglobulin replacement (see later). On the other hand, decisions about IgG supplementation in patients with less severe deficiencies often require close observation, subjective evaluation, and clinical judgement, in addition to laboratory data. A useful scheme is presented in Table 4.4. In deciding which form of therapy may be most appropriate for any given patient, the practitioner must consider not only the underlying diagnosis but also the exposure history, the cumulative morbidity and future risk for end-organ damage from infection, and the risks and adverse effects of the various therapeutic options. The number of days lost from school or work due to infection, as well as the number of days which might be required for IgG infusions at a hospital or infusion center, must be considered, along with other interferences with the patient's lifestyle. Formal pulmonary function tests and CT scans may indicate progressive, yet subclinical chronic lung disease which may mandate immunoglobulin supplementation, despite a lack of acute pneumonias. The absence of symptomatic complaints of chronic lung disease may represent accommodation and/or denial by the patient (9,62–65). Often, antibody-deficient patients who present with repeated acute infections also have systemic morbidity, about which they may or may not complain. This may include fatigue, lack of stamina, poor weight gain (in infants), gastrointestinal symptoms (primarily chronic diarrhea from lymphocytic

colitis or infection such as giardiasis), dismissed as "irritable bowel syndrome," and musculoskeletal/rheumatic symptoms that have been attributed to other causes or ignored. Because these symptoms often improve with appropriate management of chronic infection and immunoglobulin replacement, they must be carefully evaluated in the review of systems and weighed in considering the options for therapy. Patients with a history of inflammatory bowel disease, recurrent problems with *Clostridium difficile,* and/or drug allergies may have decreased tolerance for antibiotics, which can limit the alternatives to IgG therapy. Patients who present with chronic obstructive pulmonary disease and those with asthma–COPD overlap syndrome or asthma triggered by infection may actually have underlying antibody deficiencies. If so, the patient may experience a marked amelioration of lower airway symptoms and exacerbations if infection is prevented with IgG supplementation (113) and/or the astute use of antibiotics (114).

TABLE 4.4 **WHEN IS IgG REPLACEMENT/SUPPLEMENTATION INDICATED?**

- IgG < 200 mg/dL: all patients
- IgG 200 to 500 mg/dL: if specific antibody deficiency documented and frequent infections
- IgG > 500 mg/dL: if specific antibody deficiency identified and severe/recurrent infections, and/or intolerance or failure of antibiotics

IgG, immunoglobulin G.

After presentation by Dr. Anders Fasth, European Society for Immune Deficiency, Budapest, 2006.

A hierarchy of treatments may be employed across the range of severities of antibody deficiency, or sequentially in any given patient. Some patients, particularly small children, with partial antibody deficiency who have not had significant permanent end-organ damage may be managed by limiting their exposure to infectious agents (e.g., by removing them from day care or preschool) and being sure that they have received all appropriate vaccines, including conjugated polysaccharide vaccines and annual immunization against influenza. Immunization of the family and other close contacts is equally important. Measurement of specific antibody titers after administration of vaccines may provide reassurance for parents and referring physicians and may

suggest that additional therapy is not indicated. In some cases of partial antibody deficiency, immunization, prompt and rigorous treatment of likely bacterial infections such as sinusitis and bronchitis, and verification that antibiotics are continued until the infection has been completely resolved, may provide satisfactory control. Freedom from chronic or progressive symptoms should be assessed by frequent clinical follow-up. In other cases, prolonged courses of oral antibiotics and/or parenteral treatment may be required. The next step would be the use of prophylactic antibiotics (114). Many patients attain satisfactory freedom from infection by a once-daily dose of trimethoprim-sulfamethoxazole[*] (e.g., half of the total daily dose that would be used for otitis media). Other oral antibiotics, such as ampicillin or a cephalosporin, may also be used, especially in patients who are allergic to sulfonamides, but these may be associated with a higher risk for resistant bacteria. Patients who develop diarrhea or other excessive gastrointestinal side effects, oral thrush, or vaginal candidiasis may be poor candidates for this approach. Because of the possible development of antibiotic resistance, when patients on prophylactic antibiotics develop infections likely to be of bacterial origin, a full course of different agent should be used for treatment, because the prophylactic regimen may be resumed.

In patients with severe antibody deficiency, in those for which antibiotic therapy is problematic, and in those in whom prophylaxis has not been satisfactory, immunoglobulin replacement therapy is indicated (1,2,115). This can be conveniently done by the IV or subcutaneous routes (116–118). Intramuscular injections of immune serum globulin are rarely used in the current era, except as occasional prophylaxis for travelers.

Currently available immunoglobulin preparations are made from the pooled plasma of thousands of donors and contain a broad spectrum of molecularly intact specific IgG antibodies of all four subclasses, with little or no IgM or IgE (118). The content of albumin and IgA varies. Most preparations contain stabilizers such as the amino acids glycine or proline, although some contain sugars such as maltose or sucrose (Table 1 in Ref. 118). Because IgG is a blood product, the possibility of transmission of blood-borne viruses must be considered (119). This risk is minimized by careful screening and selection of donors, by the processes used to purify the IgG (usually a modification of the Cohn–Oncley cold alcohol precipitation procedure followed by one or more steps of ion-exchange chromatography), and by specific viral inactivation steps (119–123). These may include treatment with solvent–detergent, fatty acids and/or fatty alcohols to inactivate enveloped viruses (120,121,123) and pasteurization, and/or low pH incubation to denature capsid proteins of

nonenveloped viruses (121,122). Most products also undergo nanofiltration to remove viruses. Several recent comprehensive reviews of IgG therapy are available (116–118,124).

Because the average half-life of IgG in the circulation is about 21 days, IV infusions are usually given every 3 to 4 weeks (115–118,124). Alternatively, subcutaneous infusions can be given at home at intervals from daily small "pushes" to weekly or once every 2- to 4-week infusions (116,117). Preparations as concentrated as 20% reduce the volumes needed for subcutaneous therapy so that only one or two infusion sites are needed to accomplish each infusion in less than 2 hours (116,117,124). Another approach uses recombinant human hyaluronidase to transiently break down cross-links in the subcutaneous connective tissue and facilitate infusion of larger volumes of 10% IgG solution (125). Regardless of the route of administration, the dose should be individualized to control infections and other symptoms, but usually falls in a range of 300 to 800 mg/kg/month (1,2,126–130). The higher doses are often used in patients with chronic lung and/or sinus infection (116,129). Serum IgG concentrations determined at the trough, just before the next infusion, can be used to provide an index and to assist decisions about the adequacy of dose and treatment interval, but should not by themselves be used as an endpoint (1,2,129,130). In general, maintaining serum IgG levels above 500 mg/dL provides adequate protection against serious bacterial infections and is considered a minimal therapeutic target. Pooled analyses comprising 676 patients on intravenous immunoglobulin (IVIG) and 482 patients on SCIG show that higher IgG doses provide higher serum IgG levels, which in turn provide better protection from pneumonia and other infections (126,127). Similar findings were reported in a 22-year longitudinal study of 90 patients at a single center in the United Kingdom (129). Patients with polyclonal B-cell activation or paraproteins and some with CVID, IgG subclass deficiency, or specific polysaccharide antibody deficiency often require full replacement doses to maintain the full range of antibodies to remain infection-free despite pretreatment serum IgG levels within the normal range.

Antibody-deficient patients with active acute or chronic infection may experience severe systemic symptoms, including shaking chills and spiking fevers, and inflammatory reactions at the site of infection (e.g., the sinuses or airways) when they first receive IV infusions of IgG (131). It may, therefore, be preferable to defer initiation of treatment until a satisfactory course of antibiotics is started in such patients. IV infusions are generally initiated at the rate of 0.5 to 1 mg/kg/minute (0.005 to 0.01 mL/kg/minute of 10% solution) and increased in

a stepwise manner at 15- to 30-minute intervals, as tolerated, until a maximum rate of 4 to 6 mg/kg/minute is achieved. Occasional patients may tolerate rates as fast as 8 to 10 mg/kg/minute. Most stable patients can thus complete their monthly IVIG infusions within 2 to 3 hours. A minority of patients may experience adverse reactions during IV infusions, which may consist of headache, backache, flushing, chills, and/or nausea (131). In severe cases, there may be dyspnea, a sense of anxiety, and chest pain. These are usually not true anaphylactic reactions, are not mediated by IgE, and are frequently associated with increased rather than decreased blood pressure. Such reactions can usually be treated by temporarily interrupting the infusion or decreasing the rate and/or by administration of diphenhydramine, acetaminophen, or aspirin. Patients who demonstrate consistent patterns of reactions can be kept at slower rates for subsequent infusions or pretreated with the previously mentioned drugs. In rare cases, pretreatment with corticosteroids (e.g., 0.5 to 1 mg/kg of prednisone or IV methylprednisolone) may be necessary. True anaphylaxis is extremely uncommon but has been reported in a very small number of patients with IgA deficiency who have IgE antibodies against IgA (132,133). Because this is so rare, IgA deficiency should not be regarded as a contraindication against IVIG therapy in patients who also have significant deficiency of IgG antibodies, but slow starting rates and caution should be used. Rarely, aseptic meningitis, thromboembolic events, and acute renal failure have been associated with IVIG, generally when high doses (>1,000 mg/kg) are used for anti-inflammatory or immunomodulatory effects (119,131). These are rare in patients receiving conventional doses as replacement therapy for immune deficiencies. Late adverse reactions may include headache, possibly with features of migraine as well as nausea and/or fever, and may occur up to 48 hours after the infusion. These generally respond to acetaminophen, aspirin, or other nonsteroidal anti-inflammatory drugs. Occasionally, antiemetics, serotonin receptor antagonists, or other antimigraine preparations may be required. Patients with recurrent febrile reactions should be carefully evaluated for the presence of chronic infection, which should be treated with appropriate antibiotics. In many cases, the IVIG infusions are sufficiently benign to be safely given at home by a home care nurse, parent, or spouse (116,128). We usually establish the safety, maximally tolerated rate, and need for premedication in our clinic before allowing the patient to go to home care. IVIG is not irritating to the veins, and conventional preparations are not viscous or difficult to administer; hence, in-dwelling venous access devices such as a MediPort should not be required (1). If a patient is particularly sensitive to the pain of having the IV started, advance application of a local anesthetic, such as lidocaine/prilocaine (eutectic mixture of local

anesthetics [EMLA]), which is available as a cream or presaturated disk, may be helpful.

Subcutaneous IgG treatment is remarkably free from systemic adverse effects, and most patients can easily learn to administer the IgG at home (116,117,128). Usually, one-quarter of the previous monthly IVIG dose is given weekly, but with this route, individual treatment regimens can be very flexible. Frequently, one to three subcutaneous sites are used simultaneously for each infusion with a small portable pump and a tubing set that branches into one to three individual needles. For most adults, 25- to 27-gauge needles, 9- to 11-mm in length, are satisfactory, and the infusions are completed in ≤2 hours. The incidence of mild local adverse effects, most often resembling a lump or single hive, may be quite high, especially when this route is first employed (131). These reactions usually resolve within hours and become less frequent when subcutaneous treatment is continued. The subcutaneous route may be particularly preferable for patients in whom establishing venous access is difficult, those who have significant adverse effects from IV infusions, and those who live at a distance from an IV infusion facility and/or desire flexibility in scheduling their infusions to fit into their schedules of work, school, and other activities. Formal quality-of-life studies have shown that the ability to infuse at home, whether SC or IV, is appreciated by most patients and results in less overall intrusion of their disease into their lives (128).

Although prevention of acute, severe bacterial infections is the major goal of antibody replacement therapy, freedom from the symptoms of chronic infections and/or bronchiectasis can often be achieved, and many patients report amelioration of other symptoms such as arthralgia or arthritis when appropriate replacement has been achieved. The pulmonary status, chest CT scan results, or both, in all patients with significant antibody deficiencies, should be carefully documented at the beginning of therapy and followed at regular intervals, even if they become asymptomatic because subclinical lung disease may progress without chronic symptoms or acute exacerbations (62–65).

In some infants with normal lymphoid tissues and B-cell numbers, antibody deficiency may represent a maturational delay in the full range of antibody responses rather than a fixed and permanent defect (53,72). This is most likely to involve delayed development of T-independent antibody responses, such as those to bacterial capsular polysaccharides. After these patients have had a satisfactory interval with a normal or decreased incidence of infections, the IgG infusions should be stopped, and the patient's own antibody production should

be reassessed. We find it best to try such interruptions of therapy during the summer months, when the exposure to droplet-spread respiratory infection is reduced. Serum concentrations of the immunoglobulins and subclasses and specific antibody responses to vaccines can be redetermined after 2 to 3 months off therapy to allow sufficient catabolism of the therapeutic IgG so that the infant's own production can be assessed. In our experience, children whose IgG levels or specific antibody responses are not satisfactory by 5 years of age are not likely to improve in subsequent years, and this exercise is rarely productive above that age.

In summary, immune deficiencies include a range of disorders spanning a spectrum from SCID and X-linked agammaglobulinemia to disorders of immune regulation and subtle specific antibody defects. A high index of suspicion is necessary in all age groups. CVID and specific antibody deficiencies may present with symptoms of recurrent or chronic respiratory and/or gastrointestinal infections at any age, but the diagnosis is often delayed because it has not been considered. Recognition of the possibility that immune deficiency may be responsible for a patient's problems is the first step in determining whether an immunologic evaluation is appropriate. The pattern of infections and the associated historic and physical features may provide important clues to the underlying diagnosis and should be kept in mind because a progression through screening and specialized and definitive laboratory tests is pursued. Therapeutic efforts aimed at minimizing the morbidity from infection and/or correcting the underlying problem will be suggested by the specific diagnosis and should be individualized. Because subclinical chronic infection that can lead to long-term pulmonary damage may be present (62–65) and because there is an increased incidence of malignancy in patients with primary immune deficiencies (1,2,10,50–52), close follow-up is necessary. With rapid advances in our understanding of the molecular pathogenesis of these disorders, additional specific therapies lie just over the horizon.

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*Note that this would not provide satisfactory prophylaxis against *P. jiroveci (P. carinii)* infection for patients with T-cell deficiencies. Recommendations for that situation may be found in reference 112.

Evaluation of Eosinophilia

OLAJUMOKE O. FADUGBA AND ANDREA J. APTER

Eosinophilia is defined as the presence of excess numbers of eosinophils in the blood or tissues. The upper limit of normal number of eosinophils in the circulation has been variably described as approximately 400 to 500 cells/µL (1,2). Eosinophilia can be associated with allergic, infectious, inflammatory, neoplastic, or idiopathic disorders. This chapter focuses on the diagnosis, evaluation, and management of disease associated with eosinophilia.

EOSINOPHILS IN THE BLOOD

The eosinophil was first observed in peripheral blood by Wharton Jones in 1846. In 1879, Paul Ehrlich named the cell *eosinophil* because of the intense staining of its granules with acidic aniline dyes like eosin (3). The absolute eosinophil count (AEC) can be estimated by multiplying the percentage of eosinophils from the differential white blood cell (WBC) count by the total number of WBCs. Normally, 1% to 5% of blood leukocytes are eosinophils. The degree of eosinophilia can be categorized as mild (AEC 500 to 1,500/mm^3), moderate (1,500 to 5,000/mm^3), or severe (>5,000/mm^3) (1). In patients with leukopenia in another WBC, the percentage of eosinophils may be increased, but not their absolute number; this has been termed *pseudoeosinophilia* (4). Various conditions can affect the eosinophil count. The number of eosinophils in the blood has a diurnal variation, being highest at night and falling in the morning when endogenous glucocorticoid levels increase. Exogenous glucocorticoids, endogenous glucocorticoid production, stress, fever, and some bacterial and viral infections may suppress eosinophil counts (4). Thus, a condition promoting eosinophilia could be masked if it occurs in the context of such factors.

EOSINOPHILS IN THE TISSUES

Eosinophils are present in only small numbers in the circulation; they are primarily tissue-dwelling cells, with several hundred times more eosinophils in the tissues than the circulation. Eosinophils are generated in the bone marrow

and reside in the hematopoietic and lymphatic organs, such as the bone marrow, spleen, lymph nodes, and thymus (4,5). In healthy states, eosinophils are most prevalent in tissues with mucosal epithelial cells—primarily the gastrointestinal (GI) tract (not the esophagus), as well as the respiratory and lower genitourinary tracts (particularly the uterus) (6). In disease, they can accumulate in any tissue, such as the respiratory (e.g., asthma, nasal polyps, and allergic and nonallergic rhinitis with eosinophilia), cutaneous (eosinophilic cellulitis or fasciitis), GI (eosinophilia-associated GI disorders), and lower genitourinary systems (eosinophilic cystitis) (7).

The half-life of eosinophils in peripheral blood is as short as 8 to 18 hours (8), but eosinophils survive for days to weeks within tissue (4). Thus, it is important to note that blood eosinophil counts do not necessarily reflect the extent of eosinophil involvement in affected tissues in various diseases. Prolonged eosinophilia, such as in the hypereosinophilic syndrome, has been associated with end-organ damage (1).

Routine eosin staining of eosinophils may underestimate eosinophil counts in tissues. Degranulation, cytolysis, apoptosis, and necrosis alter the morphology and, thus, staining properties, of the eosinophil and its granules. Hence, immunofluorescent stains with monoclonal antibodies directed against the cationic proteins from the granules or fluorescent staining techniques based on granule autofluorescense are used to detect eosinophils in tissues (4).

MORPHOLOGY AND DEVELOPMENT OF EOSINOPHILS

In order to better understand the diagnosis and management of conditions characterized by eosinophilia, we present a brief synopsis of the morphology, development, and tissue recruitment of the eosinophil (Fig. 5.1). Eosinophils are distinguished by their bilobed nuclei and large acidophilic cytoplasmic granules that give the distinct pink color with eosin staining on microscopy (9). They are bone marrow–derived granulocyte WBCs arising from $CD34^+$ hematopoietic myelocytic progenitor cells (10). Transcription factor GATA-1 has been shown to be important for promoting differentiation of the progenitor to the eosinophil lineage (11,12). The cytokines granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), and IL-5 are associated with promoting their growth and differentiation in the bone marrow (13). IL-5, which is produced by $CD4^+$ Th2 cells (and other cells including eosinophils) and acts via the IL-5 receptor, has the most potent and specific action on eosinophils (4). IL-5

stimulates eosinophil precursors to synthesize granule proteins, and mediates eosinophil expansion, priming, recruitment, and tissue survival (9,14).
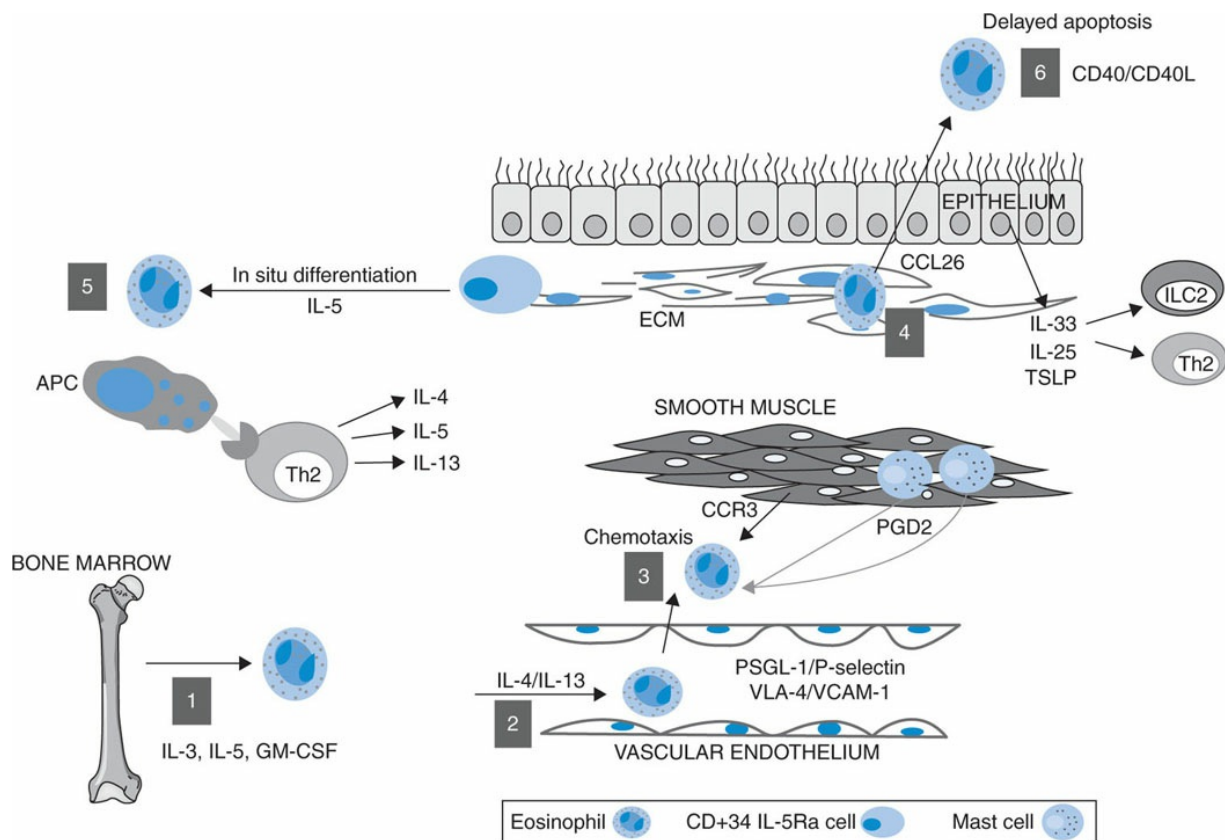

■ **FIGURE 5.1** Pathways of eosinophil trafficking (16,17). *1*, Eosinophils differentiate and mature from pluripotent CD34$^+$ stem cells in response to IL-3, IL-5, and GM-CSF. Eosinophils exit the bone marrow and enter the bloodstream where they respond to chemotactic signals. *2*, IL-13 increases expression of P-selectin and VCAM-1 on endothelial cells; these bind PSGL-1 and VLA-4, respectively, thus directing eosinophil migration. *3*, Eosinophil chemotaxis occurs by release of CCR3 (which binds chemokines such as eotaxin-3 or CCL26) from smooth muscle and PGD2 from mast cells. *4*, Eosinophils move from ECM into the airspace. *5*, CD34$^+$ IL5Rα cells differentiate into eosinophils in the lungs. *6*, IL-5 prolongs survival by preventing eosinophil apoptosis. APC, antigen-presenting cell; CCR, chemokine receptors; ECM, extracellular matrix; GM-CSF, granulocyte macrophage colony-stimulating factor; ILC, innate lymphoid cell; PGD, prostaglandin; PSGL, P-selectin glycoprotein ligand; TSLP, thymic stromal lymphopoietin; VCAM, vascular cell adhesion molecule; VLA, very late antigen. (Reprinted from Woolnough K, Wardlaw AJ. Eosinophilia in pulmonary disorders. *Immunol Allergy Clin North Am*. 2015;35:477–492.)

The migration of eosinophils and progenitor cells through the bone marrow

sinus endothelium and their release into the circulation is promoted by IL-5 and eotaxins (10,15). Eotaxins (C-C motif chemokine ligand 11 [CCL11], CCL24, CCL26, also known as eotaxin 1, 2, and 3, respectively) are chemoattractant cytokines (chemokines) that promote eosinophil recruitment to tissues via binding to chemoattractant cytokine receptor 3 (CCR3), which is expressed predominantly on eosinophils (9). Eosinophils exit the circulation and migrate to mucosal surfaces, including the lung, gut, and lower genitourinary tract (9). This migration is mediated by adhesion molecules on endothelial and eosinophil surfaces. Eosinophils bind and roll on the surface of the endothelium through binding of P-selectin glycoprotein ligand 1 (PSGL-1) on eosinophils with E- and P-selectin on endothelial cells (9,11). After rolling stops, eosinophils adhere firmly to the endothelial walls by binding of integrins to their ligands: The β_1 integrin very late antigen 4 (VLA-4) and β_2 integrin, lymphocyte function-associated antigen 1 on eosinophils bind to the vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1, respectively, on endothelial cells (9,14). Following firm adhesion to the endothelium, the eosinophil then migrates out of the vascular compartment. The migration of eosinophils into the tissues is controlled by chemoattractants. These include platelet-activating factor (PAF), complement components (C3a and C5a), leukotrienes, lipoxygenase-derived products, and chemokines. The chemoattractant effect of eotaxins is augmented by IL-5. Other chemoattractants not specific to eosinophils include RANTES (CCL5) and macrophage inflammatory protein 1α (CCL3). PGD2 released by mast cells, binds to CRTH2, which is a chemoattractant receptor expressed on eosinophils, basophils, type 2 innate lymphoid cells (ILC2), and Th2 cells (16).

The significance of ILC2, IL-33–responsive cells which reside in tissues such as the lungs and small intestine, has recently become clear (17). Epithelium-derived innate cytokines thymic stromal lymphopoietin (TSLP) and IL-33 promote eosinophil recruitment via stimulation of Th2 responses. IL-33 initiates Th2 responses by stimulating Th2 secretion of cytokines such as IL-5 and IL-13 from ILC2 (18). TSLP and IL-33 also act directly on eosinophils by preventing apoptosis and increasing survival of eosinophils (19,20).

In tissue, eosinophils modulate immune responses using a variety of mechanisms, including antigen presentation, cytokine release, and secretion of cytotoxic granule cationic proteins (21). After engagement of their receptors by cytokines, immunoglobulins (Ig), and complement, eosinophils can release an assortment of cytokines, chemokines, and lipid mediators, including PAF,

leukotriene C4, PGE2, PGE1, and thromboxane B2 (14). These factors can then cause inflammation by upregulating adhesion, altering cellular trafficking, and regulating vascular permeability, mucus secretion, and smooth muscle contraction (14,17). Although eosinophils were originally considered to be primarily effector cells participating in host defense against parasites, it is now recognized that eosinophils may also play a role in both innate and adaptive immunity. Some of the roles independent of parasite and IgE-associated responses include promotion of plasma B-cell survival (22) and directing T-cell function via eosinophil expression of MHC class II and costimulator molecules (23). Eosinophils also promote survival of alternatively activated macrophages in adipose tissue, may act as initial responders to cell death and tissue damage, and participate in remodeling and repair processes (24).

Mature eosinophils can produce their end effector toxic and inflammatory effects by the release of mediators stored in their crystalloid granules, called secondary or specific granules. The specific granules contain four major proteins: cationic major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin, and eosinophil peroxidase (EPO) (17,25). ECP is involved in pore formation in cell membranes, facilitating entry of other toxic molecules into target cells. It can also suppress T-cell proliferation and immunoglobulin synthesis, induce mast cell degranulation, and stimulate airway mucus secretion by fibroblasts (25). In the respiratory epithelium, activated eosinophil granule products can impair cilia beating and increase vascular permeability. MBP increases smooth muscle reactivity and has direct toxic effect on parasites (11). EPO generates halides which react with hydrogen peroxide formed in the respiratory burst, to produce hypohalous acids which are bactericidal (26). Eosinophil granule proteins also trigger degranulation of mast cells and basophils and amplify the inflammatory cascade by promoting release of chemoattractants, such as eotaxin, RANTES, and PAF. Eosinophil primary granules contain Charcot–Leyden crystals which are leased in high quantities in tissue in eosinophil disorders, such as sputum of asthmatics. They appear as distinct needles-shaped colorless structures (14).

DIFFERENTIAL DIAGNOSIS OF EOSINOPHILIA

Eosinophilia can be classified into primary and secondary causes (27). Eosinophilia can result from either mutation-mediated clonal expansion of eosinophils as in primary eosinophilia, or more commonly by cytokine-mediated increased differentiation and survival of eosinophils (polyclonal) as seen in secondary or reactive eosinophilia. Eosinophilia is primarily driven by IL-5

produced by Th2 lymphocytes as well as ILC-2 (28). Primary causes of eosinophilia include clonal eosinophilia resulting from a hematologic malignancy or idiopathic eosinophilia, which is a diagnosis of exclusion. Causes of secondary eosinophilia includes allergy, infection, medications, vasculitic disorders, tissue-associated inflammation, and malignant conditions in which the eosinophils are reactive and not clonal (27). Table 5.1 displays the differential diagnosis of eosinophilia in blood and tissues. A review of some of the causes of peripheral and/or tissue eosinophilia most pertinent to the allergist-immunologist and not covered in other chapters is discussed in the subsequent section. Topics include helminthic infections, drugs, hypereosinophilic syndrome (HES), eosinophilic granulomatosis with polyangiitis (EGPA), eosinophilic pneumonias, eosinophilic cystitis, and IgG4-related disease (IgG4RD). Other chapters review eosinophilic GI diseases, rhinitis, sinusitis, nasal polyps, and allergic bronchopulmonary aspergillosis. While the level of peripheral eosinophilia does not usually predict the cause, very low or high levels can provide clues—for example, very mild eosinophilia may suggest atopic disease, and a level $\geq$20,000 eos/µL may point to a myeloproliferative disorder (29).

TABLE 5.1 DISEASES MOST FREQUENTLY ASSOCIATED WITH EOSINOPHILIA OF BLOOD OR TISSUES

DISEASE	REFERENCE(S)
Infectious	
Parasitic infections (helminths)	(33)
Fungal (aspergillosis, coccidioidomycosis)	(4,41)
Retroviral (e.g., HTLV-I and HTLV-II, HIV)	(42,148)
Chronic tuberculosis	(149)
Pneumocystis carinii infection	(150)
Respiratory	

Asthma	Chapter 10
Allergic rhinitis	Chapter 10
Nonallergic rhinitis with eosinophilia syndrome	Chapter 10
Nasal polyposis	Chapter 10
Chronic rhinosinusitis	Chapter 10
Allergic bronchopulmonary aspergillosis	Chapter 10
Allergic fungal sinusitis	(151)
Acute eosinophilic pneumonia	See text
Chronic eosinophilic pneumonia	See text
Langerhans cell histiocytosis (eosinophilic granuloma)	(152)

Dermatologic

Atopic dermatitis	Chapter 10
Eosinophilic panniculitis	(153)
Eosinophilic cellulitis (Well syndrome)	(154,155)
Eosinophilic fasciitis (Shulman syndrome)	(156)
Episodic angioedema with eosinophilia (Gleich syndrome)	(60)

Eosinophilic folliculitis	(156,157)
Kimura disease	(158,159)

Vasculitic or connective tissue

Eosinophilic granulomatosis with polyangiitis	See text
Eosinophilic vasculitis	(83,160)
IgG-4 related disease	See text

Hematologic and neoplastic

Hypereosinophilic syndrome (HES)	See text
Leukemia	(161,162)
Lymphoma (Hodgkin, non-Hodgkin)	(163)
Sézary syndrome	(164)
Solid tumors (e.g., cervical tumors; large cell carcinoma of the lung; squamous cell carcinoma of skin, penis, vagina; adenocarcinoma of gastrointestinal tract; transitional cell bladder carcinoma; breast)	(2,165)
Systemic mastocytosis	(166)

Gastrointestinal

Eosinophilic gastrointestinal disorders	Chapter 10

Inflammatory bowel disease	(167,168)
Celiac disease	(167)
Cardiac	See HES
Urologic/renal	
Eosinophilic cystitis	See text
Dialysis	(169)
Immunologic	
Omenn syndrome	(170,171)
Hyper-IgE syndrome	(172)
Wiskott–Aldrich syndrome	(172)
Autoimmune lymphoproliferative syndrome (ALPS)	(172)
Transplant rejection	(173,174)
Endocrine	
Hypoadrenalism	(175)

HTLV, human T-lymphotropic virus; IgG, immunoglobulin G.

Infections and Eosinophilia: Helminthic Diseases

In developing countries, helminthic diseases are the most common cause of eosinophilia, whereas, in developed countries, atopic diseases are most common. Infections with bacteria and most viruses are generally associated with reduced eosinophils. However, respiratory syncytial virus has been shown to stimulate endothelial cells to produce eosinophil chemoattractants and activate eosinophils in lungs (30).

Helminthic infections promote eosinophilia by promoting Th2-mediated IL-4 and IL-5 production, and inducing endothelial expression of eotaxin and regulated upon activation, normal T cell expressed and secreted (RANTES) (31). However, the precise function of eosinophils in parasitic function *in vivo* is not certain. While eosinophils have been shown to be potent effectors in killing parasites *in vitro* and to aggregate and degranulate in the vicinity of damaged parasites *in vivo* (25), *in vivo* data in animal models suggest that eosinophils are often not needed, in some cases protect the host, and, in other instances, protect the parasite (32).

Helminthic diseases which cause significant eosinophilia include strongyloidiasis, ascariasis, hookworm infection (ankylostomiasis), schistosomiasis, trichinosis, filariasis (caused by *Wuchereria bancrofti* or *Brugia* species), gnathostomiasis, *Toxocara canis* infection causing visceral larva migrans, cysticercosis, echinococcosis, and paragonimiasis (33). Other helminths associated with eosinophilia include *Mesocestoides corti, Hymenolepis diminuta, Angiostrongylus* species, *Anisakis* species, *Baylisascaris* species, *Enterobius vermicularis, Heligmosomoides polygyrus, Litomosoides* species, *Nippostrongylus* species, *Onchocerca* species, *Trichuris* species, *Fasciola* species, and *Clonorchis* species (5,33). Eosinophilia has also been seen in *Plasmodium falciparum* infection (34), and infection with *Babesia* species (35). With the exception of *Isospora belli, Dientamoeba fragilis,* and *Sarcocystis* species, protozoan infections, such as Giardia, generally do not elicit eosinophilia (4). In parasitic infections associated with eosinophilia, the level of peripheral blood eosinophilia may be modest or even nonexistent if the infection is well contained in tissues, such as in an echinococcal cyst or the GI tract (4). The levels of peripheral eosinophilia may fluctuate as these cysts leak or adult filaria migrates. Blood eosinophil levels sometimes parallel the extent of tissue involvement and may be very marked as, for example, in disseminated *Strongyloides* species infection.

It is important to diagnose infection with *Strongyloides* species, located in

tropical climates and the Southeastern United States, which sometimes may be dormant and unrecognized in a patient for years. This is critical because immunosuppression and corticosteroids often used to treat eosinophilic conditions, may lead to potentially fatal dissemination of this helminth (36). Serial stool examinations with appropriate serologic tests are the initial diagnostic tests for parasites that infect the GI tract (37). Stool studies are not sensitive for strongyloidiasis because only small numbers of larvae are shed in the stool and up to seven stool studies are required to reach a sensitivity of 100% (38). Of note, helminth therapy may result in transient increase in eosinophilia, which can persist long after treatment (39).

Ectoparasites such as scabies mites, especially when severe, can cause eosinophilia (40). Fungi such as *Aspergillus*, disseminated coccidioidomycosis, histoplasmosis, and cryptococcosis can also be associated with eosinophilia (4,41). Eosinophilia can be seen with retroviral infections, particularly human T-lymphotropic virus (42). It may also occur in HIV-infected patients, but this is usually due to a secondary cause (e.g., drug, adrenal insufficiency, eosinophilic folliculitis), rather than direct induction by HIV (43).

Drug Reactions Associated with Eosinophilia

Medications are a relatively common cause of eosinophilia. Table 5.2 displays drugs that have been associated with eosinophilia; note that this is not a comprehensive list. Among the drugs most frequently reported are anti-infective medications, nonsteroidal anti-inflammatory agents, and allopurinol. Because any drug can be associated with eosinophilia, when taking a history, inquiry should be made about prescription as well as herbal and dietary supplements and over the counter agents. For example, contaminated L-tryptophan supplements have been associated with the eosinophilia-myalgia syndrome (44,45). Patients should also be asked about the use of illicit drugs because cocaine and heroin use have been associated with eosinophilia (46,47). Because many drugs are cited as case reports, it is often difficult to interpret whether or not the association between the drug and eosinophilia is causal or unrelated, and it is unclear how frequently eosinophilia occurs with the drugs.

TABLE 5.2 DRUGS ASSOCIATED WITH EOSINOPHILIA AND DRESS

ANTIBIOTICS	ANTI-INFLAMMATORY AGENTS
Penicillins	Nonsteroidal anti-inflammatory

	drugs
Cephalosporins	Allopurinol
Fluoroquinolones	Dapsone
Tetracyclines	Sulfasalazine
Linezolid	**Antihypertensives/cardiovascular agents**
Nitrofurantoin	Hydrochlorothiazide
Metronidazole	Angiotensin-converting enzyme inhibitors
Trimethoprim-sulfamethoxazole	β-Blockers
Piperacillin-tazobactam	Warfarin
Vancomycin	**Antidepressants**
Anticonvulsants	Desipramine, imipramine
Phenytoin	Amitriptyline
Carbamazepine	Fluoxetine
Phenobarbital	**Miscellaneous**
Lamotrigine	Abacavir
Valproic acid	Nevirapine

	H$_2$-blockers—ranitidine, cimetidine
	Omeprazole
	Imatinib

DRESS, drug rash with eosinophilia and systemic symptoms syndrome.

Adapted from Box 1 in Curtis C, Ogbogu PU. Evaluation and differential diagnosis of persistent marked eosinophilia. *Immunol Allergy Clin North Am*. 2015;35(3):387–402.

Eosinophilia associated with drugs may be asymptomatic or may be associated with organ involvement, such as dermatitis, acute interstitial nephritis, or eosinophilic pneumonia (48). Drug rash with eosinophilia and systemic symptoms syndrome, recently also termed drug-induced hypersensitivity syndrome, is a potentially life-threatening reaction which develops 2 to 6 weeks after drug initiation and can persist for several weeks after discontinuation (49). Findings include eosinophilia, fever, rash, lymphadenopathy, hepatic, renal failure, pneumonitis, and carditis. Although asymptomatic drug-induced eosinophilia may not warrant cessation of the drug if the benefit outweighs the risk-with organ involvement, discontinuation of the offending drug is required for resolution, and, in some cases, systemic corticosteroids may be warranted (29).

Hypereosinophilic Syndromes

HESs are a group of rare diseases characterized by persistent marked peripheral eosinophilia with end-organ involvement not attributable to other causes of eosinophilia. The definition and classification of HES has evolved over the past few decades because more information has been acquired regarding the clinical spectrum and underlying molecular pathology (50). Initially, in 1975, Chusid and colleagues proposed three diagnostic criteria for HES that formed the basis of the current diagnosis and classification system. These included persistent eosinophilia ≥1,500/μL for more than 6 months, exclusion of secondary causes of eosinophilia, and evidence of organ involvement (51).

Over the past decade, characterization of distinct phenotypes of HES has emerged, based on the clinical features, laboratory findings, complications, natural history, and therapy response. In 2006, the Hypereosinophilic Syndromes

Working Group included other disease within HES, such as EGPA, chronic eosinophilic pneumonia (CEP), and EGIDs (52). With the 2010 revisions, it was suggested that a diagnosis of HES could be made if there is an AEC > 1,500/μL on at least two occasions separated by a month, in order to reduce the progression risk of waiting the 6-month diagnostic period previously required by Chusid's criteria. In addition, the requirement for end-organ damage was removed because some patients do not develop end-organ dysfunction, and the molecular pathology underlying some forms of HES that have since been discovered, were included (53). HES can be classified into the following variants (Fig. 5.2): myeloproliferative HES (M-HES), lymphocytic HES (L-HES) (each of these account for 10% to 20% of HES cases), familial HES, organ-restricted (or overlap) HES, specific syndromes associated with hypereosinophilia, and idiopathic HES (54). These variants, organ manifestations, and treatments are discussed later.

Myeloproliferative Hypereosinophilic Syndrome

Before M-HES was specifically defined, there were descriptions of a subset of patients who were often young males with myeloproliferative features, such as hepatomegaly, splenomegaly, anemia, thrombocytopenia, elevated serum B_{12}, and tryptase; these patients were more often refractory to glucocorticoid therapy and had overall poor prognosis (50,54). This group of patients are categorized as having M-HES. After a subset of these patients were noted to have dramatic response to treatment with imatinib, a tyrosine kinase inhibitor, it was discovered that the majority of responsive patients have a gene fusion of Fip1-like 1 (*FIP1L1*) and platelet-derived growth factor receptor alpha (*PDGFRA*), or *FIP1L1-PDGFRA (F/P)* on chromosome 4q12. The F/P fusion, which can be detected by fluorescence in situ hybridization or reverse transcription polymerase chain reaction of the bone marrow or peripheral blood, leads to a constitutively active tyrosine kinase, the target of imatinib. This fusion product in one series was found in 11% of HES patients, all of whom were male (55). There are patients lacking the F/P mutation who are also responsive to imatinib; some of them have other rare abnormalities, including *KIF5B-PDGFRA* and *ETV6-PDGFRB* fusions and *PDGFRA* point mutations (54). Clonal eosinophilia has been reported in patients with Janus kinase 2 (*JAK2)* gene abnormalities and D816V KIT mutation seen in systemic mastocytosis (56). Finally, there are reports of patients termed chronic eosinophilic leukemia-not otherwise specified who have increased bone marrow blasts with clonal eosinophils not meeting criteria for other known lymphoid or myeloid neoplasm (54). In M-HES,

examination of the bone marrow reveals increased numbers of eosinophils, often 30% to 60% of marrow cells. When blast forms are present in the blood or make up more than 5% to 10% of the eosinophils in the marrow, the diagnosis is eosinophilic leukemia (50,54).
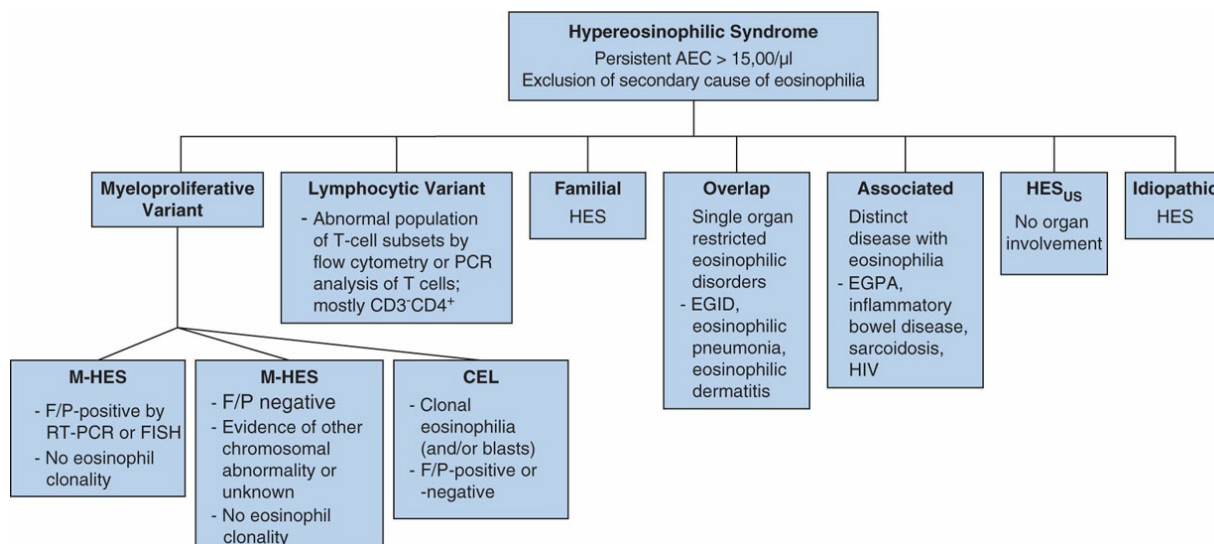
■ **FIGURE 5.2** Classification of hypereosinophilic syndromes (HESs). CEL, chronic eosinophilic leukemia; EGID, eosinophilic gastrointestinal disorders; EGPA, eosinophilic granulomatous polyangiitis; F/P, FIP1L1/PDGFRA; FISH, fluorescence in situ hybridization; HEus, HES of undetermined significance; HIV, human immunodeficiency virus; M-HES, myeloproliferative hypereosinophilic syndrome; RT-PCR, reverse transcription polymerase chain reaction. (Adapted from Simon HU, Rothenberg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome. *J Allergy Clin Immunol*. 2010;126[1]:45–49.)

Lymphocytic Hypereosinophilic Syndrome

In lymphocytic or T-lymphocytic HES, eosinophilia is driven by IL-5 produced by abnormal population of T-cell subsets, mostly $CD3^-CD4^+$ (less commonly $CD3^+CD4^-CD8^-$ or $CD3^+CD4^+CD7^-$). These can be identified in peripheral blood by flow cytometry or T-cell receptor rearrangement studies (57). Distinguishing features of L-HES include high prevalence (up to 94%) of skin and soft tissue involvement, and elevated levels of serum IgE and thymus and activation-regulated chemokine (TARC) (57,58). L-HES affects males and females equally, usually follows an indolent course, but may progress to lymphoma and requires monitoring (54). Episodic angioedema and eosinophilia (also called Gleich syndrome) represents a very rare subset of L-HES characterized by cyclic (every 28 to 32 days) episodes of urticaria and

angioedema with associated transient elevation in serum IL-5 and severe eosinophilia, which all self-resolve between episodes. These patients have clonal CD3$^-$CD4$^+$ population and often have elevated serum IgM (59,60).

Other Forms of Hypereosinophilic Syndrome

Patients with overlap HES have single organ involvement with peripheral eosinophilia. These include eosinophilic GI disorders, eosinophilic dermatitis (Well syndrome), and eosinophilic pneumonia. Distinguishing these diseases from HES is important because therapy for these disorders may not be helpful for managing multisystem HES (54). Patients with associated HES have a distinct condition, with associated eosinophilia. Examples include inflammatory bowel disease, sarcoidosis (61), IgG4RD (62), and HIV; treatment targets the underlying disorder. The familial form of HES is usually lifelong and asymptomatic, although there is a report of two members of an affected family developing fatal endomyocardial fibrosis (63). After comprehensive evaluation, greater than 50% of patients do not fall into a defined category, and are considered to have idiopathic HES. Finally, a group of patients who do not develop end-organ manifestations are described as having hypereosinophilia of undetermined significance.

End-Organ Complications of Hypereosinophilic Syndrome

The most common organ systems involved in HES include cardiovascular, cutaneous, hematologic, pulmonary, and neurologic. Cardiac manifestations are seen in up to 60% of HES cases, and can contribute significantly to morbidity and mortality (50,64). Cardiac damage is thought to progress through three stages: acute necrosis, thrombosis, and late endocardial fibrosis (65,66). The acute necrotic stage is often clinically silent, although on histology may reveal damage to the endocardium with necrosis and eosinophilic infiltration of myocardium with eosinophil degranulation products and microabscesses. Treatment in the first stage with corticosteroids may prevent progression to the other irreversible stages (66). Within approximately 1 year of the necrotic stage, the second stage is characterized by thrombi in the ventricle and, occasionally, in the atrium, likely due to hypercoagulability and endothelial disruption. In the third stage, an average of 2 years after eosinophilia onset, cardiac fibrosis may lead to entrapment of the chordae tendineae and resultant mitral, tricuspid valve insufficiency, or a restrictive or dilated cardiomyopathy. Patients may present with dyspnea, chest pain, or congestive heart failure (CHF). Because the heart is the most common site of organ involvement and because the first stage may be

clinically silent, an initial and/or a serial electrocardiogram and echocardiogram must be obtained if HES is suspected. Cardiac magnetic resonance imaging may be a more reliable test for noninvasive diagnosis of myocardial complications of HES (67).

The most common cutaneous findings, particularly with L-HES but also M-HES, are erythroderma, urticarial plaques, angioedema, pruritic papules, and nodules (66,68). Painful mucosal ulceration, which may be confused with Behcet disease, is rare, difficult to treat, and is mainly seen in M-HES (65). Patients who have urticaria or angioedema as skin manifestations tend to have a better prognosis because they are less likely to have cardiac or neurologic manifestations (65,66). Biopsy specimens of the papular and nodular lesions reveal perivascular infiltrates of eosinophils, neutrophils, and mononuclear cells without evidence of vasculitis (66).

Neurologic involvement occurs in about half of cases and has three forms: thromboembolic disease from the heart, primary central nervous system dysfunction, and peripheral neuropathy (50,69). Clinically, patients with thromboembolic events present with strokes, transient ischemic attacks, or visual symptoms. Central nervous system dysfunction can manifest as gait disturbance, behavioral changes, memory loss, or upper motor neuron signs, such as increased muscle tone. Peripheral neuropathy may be expressed as mononeuritis multiplex with symmetric or asymmetric sensory deficits, painful paresthesias, or as motor neuropathies.

About half of HES patients have respiratory findings, including cough, dyspnea, and abnormal lung imaging findings (66). Pulmonary involvement is believed to result from infiltration of lung tissue by eosinophils, less commonly fibrotic lung disease, or may originate from primary cardiac events, such as CHF or emboli from right ventricular thrombi (66,70).

Hematologic abnormalities in HES include anemia seen in up to 75% of patients in one of the National Institutes of Health series, thrombocytopenia, and hepatosplenomegaly (50). The eosinophils may have normal morphology or atypical features, including larger cells, cytoplasmic vacuoles, and both hyposegmented and hypersegmented nuclei (71). Diarrhea is the most frequent sign of GI tract involvement. Eosinophilic gastritis, enterocolitis, colitis, pancreatitis, hepatitis, and the Budd–Chiari syndrome all have been described in HES (66). Rheumatologic manifestations include eosinophilic vasculitis, arthralgias, joint effusions, arthritis, Raynaud phenomenon, and digital necrosis.

Treatment of Hypereosinophilic Syndrome

Treatment of HES requires the clinician to assess the degree of eosinophilia, urgency needed to reduce eosinophilia, end-organ damage, underlying pathophysiology, and potential treatment toxicity (50). An algorithm for the treatment of HESs (Fig. 5.3) was proposed by Klion. Urgent therapy is indicated in the case of extremely elevated eosinophil levels, signs and symptoms of leukostasis, and evidence of potentially fatal complications, including thromboembolic events or heart failure. For urgent treatment of eosinophilia, high-dose glucocorticoid at 1 mg/kg prednisone or 1 g methylprednisolone is administered, while patients with possible Strongyloides infection should receive empiric ivermectin. Eosinophilia typically responds rapidly within 24 to 48 hours. In the case of steroid-unresponsiveness and suspected myeloproliferative HES, empiric imatinib 400 mg daily can be administered. Steroid-refractory patients are more likely to have *F/P*, and response to imatinib is expected within 1 to 2 weeks. *F/P*-negative HES patients may require a higher dose up to 800 mg, can take up to 4 weeks or longer, or may not respond at all—particularly if they have lymphocyte-variant HES (50,54).
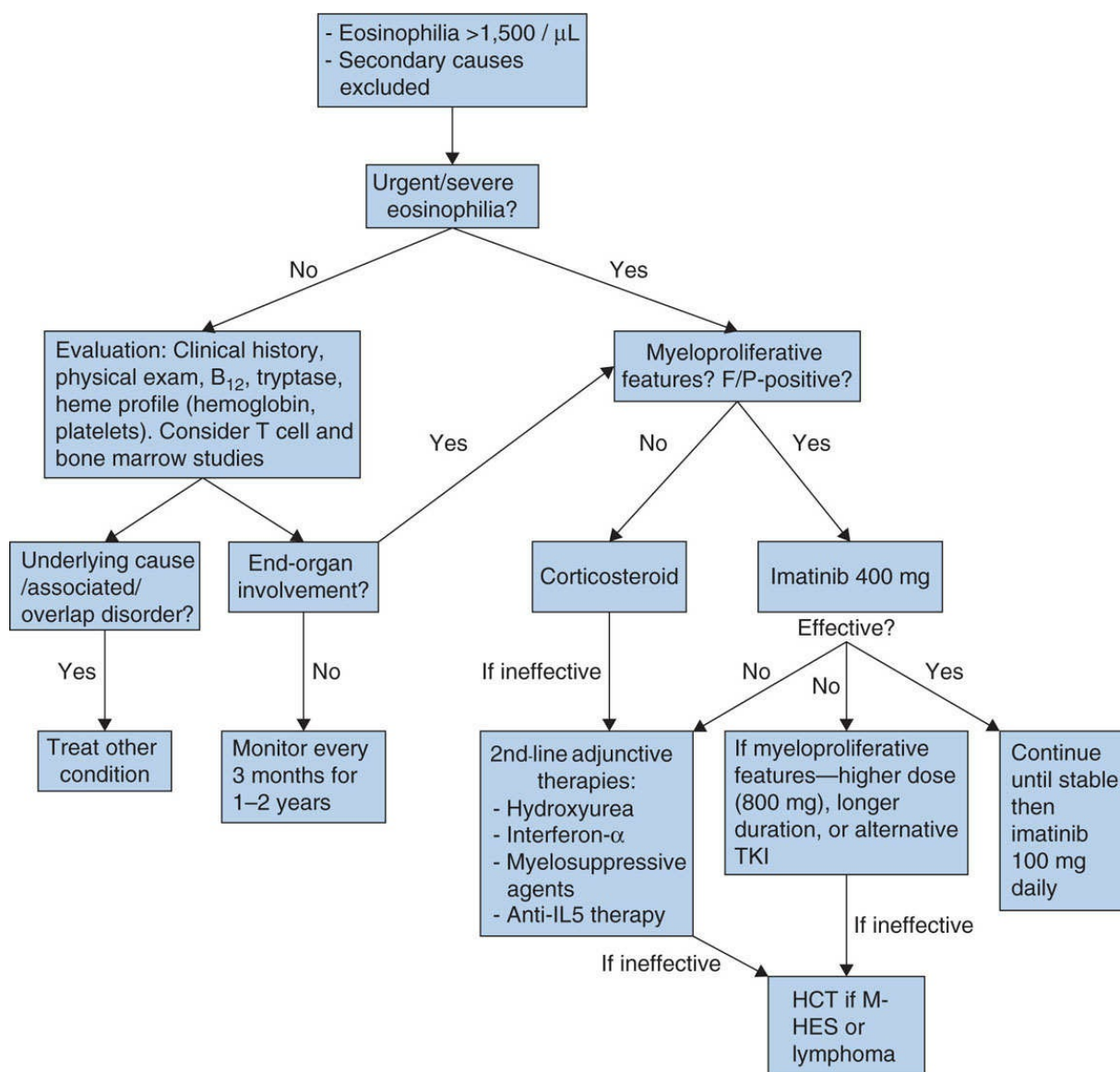
■ FIGURE 5.3 Management algorithm for hypereosinophilic syndrome. F/P, FIP1L1/PDGFRA; HCT, hematopoietic cell transplantation; M-HES, myeloproliferative hypereosinophilic syndrome; TKI, tyrosine kinase inhibitors.

First-line therapy for *F/P* M-HES (as well as *PDGFRB* rearrangements), whether urgent or stable, is imatinib—with steroids if there is cardiac involvement (72). With *F/P,* virtually all patients achieve complete remission. Typically, after the initial 400 mg dosage, patients require maintenance dosing at 100 mg daily indefinitely after remission, but there are reported cases of prolonged remission after stopping (73). In the rare cases of imatinib resistance, associated with T6741 mutation, other tyrosine kinase inhibitors, including sorafenib, nilotinib, and dasatinib, have been used in case reports (54).

Other forms of HES are treated with first-line corticosteroids. If eosinophilia is unresponsive to corticosteroids and/or imatinib therapy, second-line, steroid-

adjunctive agents should be considered. Hydroxyurea, which is easily accessible and inexpensive, is administered orally at 500 to 2,000 mg/day. It acts by impairing eosinophil development, hence can take up to 2 weeks to be effective. Vincristine 1 to 2 mg/m^2 intravenously weekly to monthly, can lower extremely high eosinophil counts. Interferon-α, which has effects on eosinophils and T cells, can be used as adjunctive therapy (with corticosteroids) in various forms of HES, including L-HES and idiopathic HES, but is limited by its significant side-effect profile (74). Alemtuzumab, an anti-CD52 antibody, is effective in some cases of HES, but is not curative and can cause severe cytopenias and immunosuppression, and is now withdrawn from the US market with limited access (75). Other cytotoxic therapies, including cyclophosphamide, methotrexate, cyclosporine, azathioprine, cladribine, and chlorambucil, have been used in case reports (50,74).

Novel therapies for HES not responsive to the first- and second-line therapies include mepolizumab, which is a humanized monoclonal antibody against IL-5. It has been used in other eosinophilic conditions, including asthma, eosinophilic esophagitis, and EGPA. The effectiveness and safety of mepolizumab in *F/P*-negative HES patients has been demonstrated in clinical trials, but it is not currently Food and Drug Administration approved (76,77). Benralizumab, an anti-IL5 receptor monoclonal antibody and neutralizing antibodies to CCR3 and CCL11 (CCR3 ligand), are also under investigation in clinical trials (50). Allogeneic nonmyeloablative hematopoietic cell transplantation (HCT) can be curative in those with refractory disease, particularly imatinib-resistant *PDGFRA*-associated HES, or L-HES with associated T-cell lymphoma. This is not a routine option owing to the potential morbidity and mortality of HCT (74).

Eosinophilic Granulomatosis with Polyangiitis

EGPA, formally called Churg–Strauss syndrome and allergic angiitis and granulomatosis, is a small and medium vessel vasculitis characterized by eosinophilia, asthma, and other organ manifestations. The estimated incidence of EGPA is about 0.11 to 2.66 cases per 1 million people per year, with an overall prevalence of 10.7 to 14 cases per 1 million adults (78–82). However, the true incidence of EGPA is likely unknown because of diagnostic uncertainties, and it is not always readily recognized. The mean age at diagnosis is 40 to 50 years. It affects men and women equally (83). EGPA is uncommon in children and people older than 65 years of age. When it does occur in children, the course tends to be more aggressive (84).

The precise pathogenesis of EGPA is unknown, but it likely derives from an autoimmune mechanism involving endothelial cells and leukocytes (85). Although antineutrophil cytoplasmic antibodies (ANCA) have been detected in approximately half of EGPA patients, its role in the pathogenesis of the disease is not established (86). Immune system factors which may play a role in the pathogenesis of EGPA include Th2 presence (87), Th1 involvement particularly with granuloma formation (88), eosinophil dysregulation (increased recruitment and decreased apoptosis) (89), and a possible role of reduced IL-10 producing T-regulatory cells (90). EGPA has been associated with various asthma medications, including leukotriene antagonists, inhaled glucocorticoids, and omalizumab (91–93). However, it is more likely that the addition of these asthma therapies in the setting of evolving EGPA allowed systemic corticosteroids to be tapered, unmasking EGPA symptoms. Despite this, a causal link cannot be ruled out.

One of the most commonly used diagnostic criteria for EGPA was formulated by the American College of Rheumatology. It yields a sensitivity of 85% and a specificity of 99.7%, if four of the following six criteria are satisfied (94): asthma, peripheral eosinophilia (>10%), mononeuropathy or polyneuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormality, and biopsy containing a blood vessel with extravascular eosinophils. The Lanham criteria require all the following three criteria: asthma, eosinophil count greater than 1,500/µL, and vasculitis involving at least two extrapulmonary organs (95).

There are three clinical phases in EGPA patients, which may not be easily distinguished practically (95). In the prodromal phase, patients have asthma and other atopic disease such as allergic rhinitis; these precede the development of the other manifestations by a mean of 8.9 ± 10.9 years (96). In the eosinophilic phase, patients have peripheral eosinophilia and eosinophilic infiltrates in various organs. The vasculitic phase is often accompanied by constitutional symptoms, such as fever, malaise, and weight loss, and can involve potentially fatal systemic vasculitis of small and medium vessels. This phase typically begins years after asthma is diagnosed but sometimes occurs within months of the diagnosis of asthma.

While EGPA can affect almost any organ, the lung, peripheral nervous system, and skin are the most commonly involved (97). Virtually all patients have pulmonary involvement, with over 90% having the cardinal feature of asthma, which may become increasingly refractory to treatment. Other lung manifestations include fleeting pulmonary infiltrates and other nonspecific

abnormalities (96). Allergic rhinitis occurs in about 75% of patients and is frequently an early symptom. Recurrent sinusitis, nasal polyps, nasal obstruction, and serous otitis media may also be seen (98). Peripheral nervous system involvement is seen in up to 80% of patients, and mononeuritis multiplex is the most common form of neurologic involvement (96,99). Skin manifestations are commonly seen in the vasculitic phase, and include palpable purpura, nodules, pustules, urticaria, and livedo (96). Skin biopsy shows leukocytoclastic vasculitis, and nodules are seen as granulomas. Cardiac manifestations, which accounts for half of deaths from EGPA, include CHF, eosinophilic endomyocarditis, coronary vasculitis, valvular heart disease, pericarditis, pericardial effusions, and dysrhythmias (97,99). In one review, almost two-thirds of patients were found to have findings at autopsy, including fibrosis, myocarditis, pericarditis, and eosinophilic granulomas in the pericardium (99). In one series, patients with cardiac involvement were more likely to have higher peripheral eosinophil count and more likely to be ANCA negative (100). The most common GI symptoms are abdominal pain, nausea, vomiting, diarrhea, and hematochezia. Ulcers and bowel perforation are rare (101,102). Renal disease, seen in 22% in the largest series of EGPA (97), is most commonly manifested as proteinuria. The degree of renal insufficiency is typically not severe (96). Patients with glomerulonephritis are more likely to be ANCA positive. Renal biopsy has shown pauci-immune focal segmental glomerulonephritis with necrosis or crescent formation (98). Myalgias and arthralgias are the most common musculoskeletal symptoms; however, true arthritis is rare (99).

Laboratory studies reveal fluctuating peripheral blood eosinophilia >1,500/ μL, with peaks between 20% and 90% of the WBC. Perinuclear ANCA (p-ANCA) directed against myeloperoxidase occur in 40% to 60% of patients. The erythrocyte sedimentation rate and C-reactive protein are frequently elevated, but are not specific for EGPA. Anemia and elevated total IgE are often present (98). Chest X-ray findings include bilateral transient patchy consolidations in a nonsegmental distribution, hilar infiltrates, diffuse interstitial opacities, and noncavitating nodular opacities (103). High-resolution computed tomography (HRCT) abnormalities include bilateral ground-glass opacities, peripheral airspace consolidation, and peribronchial and septal thickening (86,103). Bronchioalveolar lavage (BAL) in a patient with interstitial infiltrates may reveal high percentage of eosinophils. It is more practical to biopsy a noninvasive site such as skin or nerve, but if lung tissue is required, a surgical lung biopsy, the gold standard for EGPA, is more useful than a transbronchial biopsy. Biopsy of involved tissues is characterized by eosinophil infiltration, necrotizing vasculitis

of the small arteries and veins, eosinophils, and extravascular granulomas (104). The histopathologic findings can vary depending on the disease phase. An electrocardiogram and echocardiogram should be performed on all patients with EGPA to assess for cardiac involvement.

Without treatment, the prognosis is poor with 50% dying within 3 months of the onset of vasculitis (105). With modern treatment options, survival rate has improved to 70% to 90% at 5 years and up to 90% initial remission rate with relapse between 41% and 81% off immunosuppressive therapy (106–108). The patients at risk for a poor outcome are those with myocardial involvement, severe GI symptoms (intestinal bleeding, perforation, pancreatitis, or requiring laparotomy), renal insufficiency, or a short duration of asthma before the presentation of the vasculitic phase (96,98). A revised five-factors score system also includes age over 65 and absence of ear/nose/throat manifestations as poor prognostic indicators (109).

In patients without systemic involvement or indicators of poor prognosis, therapy consists of corticosteroids alone with prednisone 1 mg/kg for 2 to 4 weeks, then gradual taper to the minimal effective dose over the course of a year if no disease activity recurs (110). If there is systemic involvement or indicators of poor prognosis, cyclophosphamide is given either orally (2 mg/kg/day) or via intravenous pulses (0.6 mg/m^2 every 2 to 3 weeks) concurrently with steroids (110). Other potential treatment regimens for steroid-sparing maintenance or milder disease have included intravenous immunoglobulin, cyclosporine, interferon-α, mycophenolate mofetil, methotrexate, and azathioprine (52). Biologic therapies, including rituximab (anti-CD20) (111,112), omalizumab (anti-IgE) (113), and mepolizumab (anti-IL5) (114,115), have been used successfully in EGPA.

Eosinophilic Pneumonias

The eosinophilic pneumonias are a group of pulmonary diseases characterized by pulmonary eosinophilic infiltrates with or without peripheral blood eosinophilia (116). Eosinophilic lung disorders can be classified as acute (less than 1 month), chronic (greater than 1 month), or transient (Löffler syndrome). It can be secondary to a known specific cause such as drug reaction, infection, malignancy, or other pulmonary conditions such as asthma, or can be idiopathic. It can be isolated to the lung or occur as part of a systemic disease. Drug-induced pulmonary eosinophilia (48,117), EGPA, and HES with pulmonary eosinophilia have been discussed in this chapter. Allergic bronchopulmonary aspergillosis is

discussed in Chapter 10.

Four eosinophilic pneumonias have not been previously discussed: tropical pulmonary eosinophilia, Löffler syndrome, CEP, and acute eosinophilic pneumonia (AEP). Tropical pulmonary eosinophilia is thought to be a hypersensitivity response to filarial parasites, *W. bancrofti* and *Brugia malayi* (116). It is characterized by paroxysmal cough, dyspnea, and wheezing predominantly at night, with marked peripheral eosinophilia and diffuse reticulonodular infiltrates on chest radiographs (118). Diagnostic criteria include appropriate exposure history such as a mosquito bite after travel to an endemic area of filariasis, a history of paroxysmal nocturnal cough and dyspnea, pulmonary infiltrates, leukocytosis with eosinophilia >3,000/µL, increased serum IgE, serum antifilarial antibodies (IgE and/or IgG), and a clinical response to diethylcarbamazine citrate (116,118).

Löffler syndrome, or simple pulmonary eosinophilia, is characterized by fleeting migratory infiltrates, peripheral blood eosinophilia, low-grade fever, dry cough, wheezing, and dyspnea (116). Three helminth larvae have transpulmonary passage before reaching the GI tract: *Ascaris lumbricoides* (most common), hookworms, and *Strongyloides stercoralis* (119). Other parasite infections can be accompanied by pulmonary eosinophilia via mechanisms distinct from that described above, including *Paragonimus, Trichinella*, and *Schistosoma* (120). Most patients with Löffler syndrome have either a parasitic infection or drug reaction, although no cause can be found in about one-third of cases (121). The condition typically self-resolves spontaneously within 4 weeks.

Idiopathic CEP has an insidious onset of symptoms, including cough, dyspnea, malaise, fever, and weight loss (117). The cough, which affects up to 90% of patients, is initially nonproductive, but may become productive. Wheezing occurs in half the cases with respiratory failure being extremely rare (122). Women are affected twice as often as men (116). Although CEP may affect every age group, patients are generally at least 30 years old (122). Many have a history of atopy, and up to two-thirds have a history of asthma (122). There has been an association in some patients with prior radiation for breast cancer (123). The course is chronic, with symptoms usually present for weeks to months before diagnosis (116,117).

Blood eosinophilia is present in 66% to 95% of patients, but its absence does not exclude the diagnosis of CEP (116). BAL cell count consists of more than 25% eosinophils (often greater than 40%), a key diagnostic criteria of CEP (117). The classic chest radiograph reveals progressive peripheral dense alveolar

infiltrates, which resemble a "photographic negative" of pulmonary edema (124). However, this finding occurs in less than half of patients. Other less common radiographic findings may include nodular infiltrates, atelectasis, unilateral or bilateral involvement, pleural effusion, and rarely cavitation (117). HRCT of the chest may identify peripheral infiltrates, bilateral confluent consolidations, and ground-glass opacities in the upper lobes and subpleural regions (122,125). Pulmonary function tests may reveal a restrictive, normal, or obstructive pattern (122). The diffusion capacity of the lungs for carbon monoxide is frequently reduced. Lung biopsy is not necessary for diagnosis of CEP, but histopathologic examination reveals a predominantly eosinophilic infiltrate involving the alveoli and interstitium. Interstitial fibrosis, bronchiolitis, and bronchiolitis obliterans can be present, and, occasionally, eosinophilic microabscesses and noncaseating granulomas are observed. Necrosis is rare. Symptoms and pulmonary infiltrates resolve rapidly with initiation of corticosteroids, usually 0.5 to 1 mg/kg of prednisone for 4 to 6 weeks followed by a taper. The duration of treatment should be 6 to 9 months but, in some cases, may require up to 3 years (116). Relapses are very responsive to reinstitution of steroids (116,122). Although the prognosis is excellent, up to 50% of patients experience a relapse (122,124,126).

Idiopathic AEP has a rapid onset, and is characterized by hypoxemia and respiratory failure with profound eosinophilia on bronchoalveolar lavage fluid. Patients commonly present with fever, cough, tachypnea, dyspnea, chest pain and myalgia of less than 7 days duration, mimicking acute respiratory distress syndrome, or infectious pneumonia (117). However, the largest published case series reported patients with a duration of symptoms of up to a month before presentation (127). AEP typically occurs in previously healthy patients, and up to 70% of affected patients are smokers (128). There is equal to slight male predominance in contrast to the female predominance of CEP. AEP is a diagnosis of exclusion; hypersensitivity reactions, reactions to medications and toxins, and infectious etiologies must be ruled out. Various inhalational exposures have been associated with AEP, including World Trade Center dust, indoor renovation work, gasoline tank cleaning, tear gas, firework smoke, cave exploration, woodpile moving, plant repotting, crystal methamphetamine smoking, cocaine and heroin inhalation, and, most frequently, new-onset tobacco smoking (127–133).

Early radiographic findings of AEP show reticular or ground-glass infiltrates with Kerley B-lines and small pleural effusions. Subsequent findings include mixed reticular and alveolar infiltrates with progression to dense alveolar

infiltrates (128). HRCT of the chest demonstrates any combination of the following: diffuse interstitial infiltrates, patchy alveolar infiltrates, diffuse ground-glass infiltrates, interlobular septal thickening, bilateral pleural effusion, or alveolar consolidation (128,134).

Patients with AEP generally lack peripheral blood eosinophilia at presentation, but most develop this later in the disease course (127,128). BAL eosinophilia greater than 25% is a key feature of AEP (117). TARC/CCL17 has been suggested as a possible peripheral blood marker to help differentiate AEP from other acute lung injuries because its level is elevated in the acute phase before peripheral eosinophilia is present (135). In addition, a lower level of KL-6, a marker of alveolar cell damage, and elevated fraction of exhaled nitric oxide may also help to distinguish AEP from other acute lung injuries (135,136). Lung biopsy in not necessary for diagnosis, but histopathology is characterized by marked infiltration of eosinophils in the interstitium and alveolar spaces with common findings, including diffuse alveolar damage with hyaline membranes, fibroblast proliferation, interstitial edema, and basal lamina damage (128,137). Pulmonary function testing may reveal a restrictive defect with reduced diffusion capacity (117).

The treatment for AEP is respiratory support and high-dose corticosteroids. Recommended regimens have consisted of methylprednisolone 60 to 125 mg every 6 hours until respiratory failure resolves and then a total oral corticosteroid course of 2 to 12 weeks duration (116,128). There have been reports of some patients recovering without corticosteroids (127,138), but they are generally recommended for all patients. Most patients recover without long-term complications, and relapse is extremely rare.

Eosinophilic Cystitis

Eosinophilic cystitis is a rare disease characterized by urinary frequency, hematuria, suprapubic pain, and urinary retention (139,140). It is distributed equally between males and females, but in childhood, males are more commonly affected. Peripheral eosinophilia was present in 43% of patients in one series (140). Cystoscopy reveals hyperemic mucosa with areas of elevation and nodularity. Biopsy is characterized by eosinophilic infiltrate, mucosal edema, and muscle necrosis. This inflammatory pattern may progress to chronic inflammation and fibrosis of the bladder mucosa and muscularis. Cases have been associated with transitional cell carcinoma of the bladder, intravesical chemotherapy, various medications, allergic respiratory disease, bladder outlet

obstruction, autoimmune disorders, nonurological parasitic disorders, and eosinophilic enteritis (141). No underlying etiology was noted in 29% of patients in one series (141). Recommended treatment includes observation of mild cases, oral antihistamine, nonsteroidal anti-inflammatory agents, and systemic corticsoteroids. In cases that are refractory, severe, or with mass effect, surgical intervention such as tumor resection or cystectomy may be undertaken. (139,140).

IgG4-Related Disease

IgG4RD is one of several connective tissue disorders which may present with eosinophilia. IgG4RD is an increasingly recognized group of inflammatory disorders which can involve many different organs. These include autoimmune pancreatitis, retroperitoneal fibrosis, IgG4-related sclerosing cholangitis, IgG4-related dacryoadenitis and sialadenitis, and Riedel thyroiditis (83). These diseases share features such as tumor-like appearance in the affected organ, lymphoplasmacytic infiltrate with high number of IgG4-positive plasma cells, fibrosis with a storiform pattern, tissue with mild-to-moderate eosinophilia, and elevated tissue IgG4. Elevated serum IgG4 is seen in 60% to 70% of patients (142,143). Th2 responses are predominant, and a high proportion of patients have a history of allergic rhinitis, asthma, peripheral blood eosinophilia, and serum IgE elevation (62). The true epidemiology is not yet known, but, in a Japanese series, prevalence was 2.2 per 100,000 persons, with a male to female ratio of 3.7:1 and mean age of 63 years (144). First-line treatment consists systemic corticosteroids. In some cases, nonsteroid immunosuppressive agents and rituximab have been used with limited experience (83,145).

EVALUATION OF THE PATIENT WITH EOSINOPHILIA

The most important factor in the evaluation of a patient with eosinophilia (Fig. 5.4) is a thorough history with careful attention to medical, travel, dietary, occupational, and medication history. A history consistent with atopy and possible family history of diseases associated with eosinophilia should be elicited. If parasitic disease is a consideration, multiple examinations of the stool and appropriate serologic tests based on travel history should be ordered. Review of systems identifying organ involvement should be obtained. Physical examination with particular attention to skin, lymphadenopathy, hepatosplenomegaly, and possible masses should be performed (146). Laboratory tests and diagnostic studies to assess for hematologic and organ

involvement should be performed. The labs and diagnostic tests depend on the suspected disease and potential organ involved. An echocardiogram and chest radiograph or CT may be indicated. If the etiology remains unclear and/or the degree of eosinophilia is substantial, further examination for lymphoproliferative disease and HES should be pursued. Patients with persistent eosinophilia without a clear etiology should be monitored for evidence of end-organ damage (147).
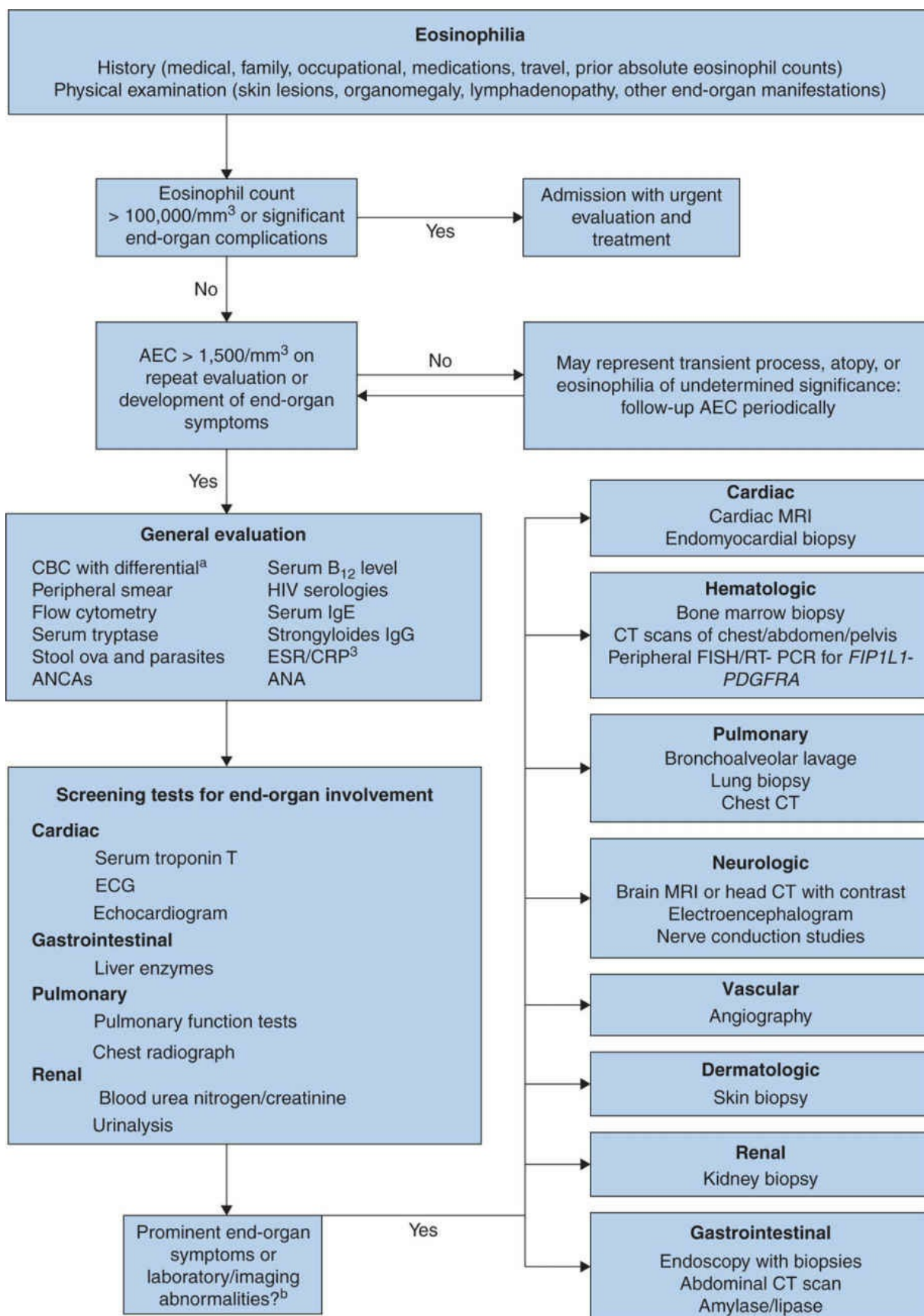
FIGURE 5.4 Algorithm for evaluation of eosinophilia. [a]Studies that may be affected by concurrent steroid use. [b]Other studies for end-organ involvement

may be warranted based on clinical presentation. AEC, absolute eosinophil count; ANA, antinuclear antibody; CBC, complete blood count; CRP, C-reactive protein; CT, computed tomography; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FISH, fluorescent in situ hybridization; MRI, magnetic resonance imaging; RT-PCR, reverse transcription polymerase chain reaction. (Reprinted from Curtis C, Ogbogu P. Evaluation and differential diagnosis of persistent marked eosinophilia. *Immunol Allergy Clin North Am*. 2015;35:387–402.)

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Pathogenic and Environmental Aspects in Allergy and Asthma

Allergens and Other Factors Important in Atopic Disease

RAVI K. VISWANATHAN, GREGORY D. BROOKS, AND ROBERT K. BUSH

An allergen is an antigen that evokes a clinical allergic reaction. In atopic diseases, allergens are antigens that elicit an immunoglobulin E (IgE) antibody response. Sensitivity to an allergen can be demonstrated by a wheal-and-flare reaction to that antigen in a skin test, or by *in vitro* immunoassays such as the radioallergosorbent test (RAST), or enzyme-linked immunosorbent assay (ELISA), which measures antigen-specific IgE in serum. RAST testing has fallen out of favor in the past decade and has been replaced by more sensitive fluorescence-enzyme-labeled assays. When assessing the contribution of a particular antigen to an observed symptom, the nature of the immune response must be clarified. The clinician must differentiate the allergic (or atopic) response from the irritant response. The immediate type I IgE-mediated allergic response is distinctly different from the type IVa pathophysiologic mechanism mediating the delayed hypersensitivity reactions, which result from contact antigens, such as poison ivy or nickel.

Allergens most commonly associated with atopic disorders are inhalants or

foods, reflecting the most common entry sites into the body through the respiratory or gastrointestinal tract. Drugs, biologic products, insect venoms, and certain chemicals also may induce an immediate-type hypersensitivity reaction. In practice, however, most atopic reactions involve pollens, fungal spores, house dust mites, animal epithelial materials, and other substances that impinge directly on the respiratory mucosa. They cross-link IgE antibodies attached to mast cells or basophils, initiating an inflammatory milieu that results in mediator release and allergic symptoms. This chapter is confined to the exploration of these naturally occurring inhalant substances; other kinds of allergens are discussed elsewhere in this text. Aeroallergens are airborne proteins that can cause respiratory, cutaneous, or conjunctival allergic symptoms. It is common for a single airborne particle, such as a mold spore or a pollen grain, to contain multiple allergens.

AEROALLERGENS

Certain aeroallergens, such as animal danders, house dust mites, and fungi, may be localized to individual homes. Others may be associated with occupational exposures, as is the case with bakers who inhale flour. Some sources of airborne allergens are narrowly confined geographically, such as the mayfly and the caddis fly, whose scales and body parts are a cause of respiratory allergy in the eastern Great Lakes area in the late summer.

Several methods can be used to determine whether a protein is an allergen. The most clinically relevant method is an allergen challenge. In a conjunctival or nasal challenge, the extract is introduced directly to the affected mucosa to look for typical allergy symptoms. In a bronchoprovocation challenge, the allergen is inhaled and pulmonary function is performed to determine when and if the FEV_1 declines by more than 20%. These methods are generally too impractical to perform in an office setting. Most often, a skin test (percutaneous or intradermal) is performed to determine whether an extract can elicit the typical wheal-and-flare response. Finally, tests to estimate allergen-specific IgE can be performed with patient sera. Although most tests are performed with crude extracts, specific IgE tests can be performed on serum to examine individual allergenic proteins within an extract. From a practical standpoint, it is the presence of specific IgE to a protein in the sera of clinically allergic patients that defines it as an allergen.

The chemical nature of certain allergens has been studied intensively, although the precise composition of many other allergens remains undefined. For an increasing number of allergens, the complementary DNA (cDNA) sequence

has been derived. For others, the physiochemical characteristics or the amino-acid sequence is known. Still other allergens are known only as complex mixtures of proteins and polypeptides with varying amounts of carbohydrate. Details of the chemistry of known allergens are described under their appropriate headings.

The methods of purifying and characterizing allergens include biochemical, immunologic, and biologic techniques. The methods of purification involve techniques such as chromatography, immunoprecipitation, and molecular biology. All of these purification techniques rely on sensitive and specific assay techniques for the allergen as reviewed here.

Allergen Nomenclature

To be recognized as an allergen by the International Union of Immunological Societies (IUIS), a protein must have evidence of allergenicity in at least five individuals or 5% of the population studied with ideally at least 50 patient sera being screened (1). Allergens to a specific source such as ragweed pollen or cat dander can be classified as either major or minor allergens. Major allergens are those that elicit specific IgE in greater than 50% of the population sensitized to the source. Minor allergens are those that result in specific IgE in less than 50% of those individuals sensitized to the specific source. Sometimes authors refer to allergens that result in specific IgE in about 50% of the sensitized population as intermediate allergens.

The nomenclature for individual allergen proteins may have been originally conceived by a meeting of the minds on a boat ride on Lake Boedensee (Germany) by Dr. David Marsh, Dr. Henning Lowenstein, and Dr. Thomas Platts-Mills in 1980. A formal naming system has since been established and maintained by the IUIS: the first three letters of the genus, followed by the first letter of the species, and an Arabic numeral (2). For example, the primary allergen in cat (*Felis domesticus*) is *Fel d 1*. Prior to the adoption of this nomenclature system, grass allergens, ragweed allergens, cockroach allergens, and dust mite allergens all had separate naming systems, that are now only of historical interest. The numbering given to the allergen is often adjusted to account for proteins in separate species that are either cross-reactive or structurally similar. The nomenclature of the German cockroach (*Blattella germanica*) and the American cockroach (*Periplaneta americana*) allergens illustrates this principle well (see Table 6.6). Notice that *Bla g 6* and *Per a 6* are both members of the Troponin C family of molecules. *Bla g 1* and *Per a 1* have

similar attributes as well. As allergenic proteins are matched by number, they often must be assigned new names, which can lead to confusion when reading even relatively recent journal articles. An updated list of all established allergens with reference to obsolete names is maintained by the IUIS (1).

Isoallergens are proteins within a species that have similar immunologic properties and/or molecular structures, but differ in some way such as isoelectric point, carbohydrate content, or amino-acid composition. For example, the ragweed allergen *Amb a 1* has four isoallergenic variants based on biochemical studies and cDNA analyses (1). The *Amb a 1* isoallergen sequences all have the same first 25 proteins, but vary in the rest of their structure.

Sampling Methods for Airborne Allergens

Patients commonly seek out daily reports of pollen or mold spore levels from the newspaper, radio, television, Internet, or via apps on the smartphone (3,4). They often use these levels to correlate and predict their allergy symptoms. It is important to understand that all of the current methods for reporting these levels involve averaging pollen levels from the day before. Thus the levels may be helpful in correlating previous symptoms but are of limited use in correlating current symptoms or predicting future symptoms. There are commercial companies that claim to have computer models that predict pollen counts. However, there are no publications that have prospectively determined the value of computer models in predicting pollen counts (5,6).

Aerobiological sampling attempts to identify and quantify the allergenic particles in the ambient atmosphere, both outdoors and indoors. Commonly, an adhesive substance is applied to a microscope slide or other transparent surface, and the pollens and spores that stick to the surface are microscopically enumerated. Devices of varying complexity have been used to reduce the most common sampling errors relating to particle size, wind velocity, and rain. Fungi also may be sampled by culture techniques. Although many laboratories use various immunoassays to identify and quantify airborne allergens, the microscopic examination of captured particles remains the method of choice. Two types of sampling devices are most commonly used: impaction and suction. Gravitational samplers were used historically, but are rarely used today because they provide qualitative data not quantitative. Several factors are important to consider with regard to placement of an outdoor sampler: local architectural obstruction, airflow patterns and prevailing wind directions, and agrarian activities. The location of samplers is important. Ground level is usually

unsatisfactory because of liability, tampering, and similar considerations. Rooftops are used most frequently. The apparatus should be placed at least 6 m (20 ft) away from obstructions and 90 cm (3 ft) higher than the parapet on the roof.

For indoor sampling, an understanding of the interior architecture and heating, ventilation, and air conditioning that is in place is necessary. The property of the allergen or particle being counted and reservoir need to be understood in choosing the appropriate sampler.

Impaction Samplers

Impaction samplers are the most common outdoor allergen samplers. Rotating arm impaction samplers have two vertical, adhesive-coated collecting arms mounted on a crossbar, which is rotated by a vertical motor shaft. Small particles, particularly pollen grains, are prone to blowing in the wind in a way that interferes with gravitational settling. They become more likely to impact on an adhesive surface. The sampler rotates up to several thousand revolutions per minute to overcome the effects of wind. However, at this speed turbulence may "push" the pollen away and decrease sampling. For this reason, the sampling surface is small (1 to a few millimeters) to get the highest rate of impaction. Small surface areas, however, are rapidly overloaded, causing a decrease in the efficiency of capture. These samplers usually are run intermittently (20 to 60 seconds every 10 minutes) to reduce overloading. In some models, the impacting arms are retracted or otherwise protected while not in use. The Rotorod sampler (Fig. 6.1) is a popular commercially available impaction sampler and has been shown to be over 90% efficient at capturing pollen particles of approximately 20 μm diameter. It is much less efficient at capturing smaller particles, especially those <5 μm diameter (7).

Suction Samplers

Suction samplers or cascade impactors employ a vacuum pump to draw the air sample into the device. Although suitable for pollens, they are more commonly used to measure smaller particles such as mold spores. Disorientation with wind direction and velocity skews the sampling efficiencies of particles of different sizes. For example, if the wind velocity is less than that generated by the sampler, smaller particles are collected in greater concentrations than what exist in the ambient air. The reverse is true for greater wind velocities. The Hirst spore trap (8) is an inertial suction sampler with a clock mechanism that moves a coated slide at a set rate along an intake orifice. This enables discrimination of diurnal variations. A wind vane orients the device to the direction of the wind.

The Burkard spore trap collects particles on an adhesive-coated drum that takes 1 week to make a full revolution around an intake orifice. Both of these spore traps are designed to measure nonviable material. Spore traps are the most flexible devices for sampling particles over a wide range of sizes.

TABLE 6.1 TREE AND WEED POLLEN ALLERGENS

	FLOWERING PERIOD	Bet v 1–LIKE PROTEIN (PR-10)	PROFILIN	POLCALCIN	PHENYLCOUMARAN BENZYLIC ETHER REDUCTASE-LIKE	POl
Tree Pollen						
Birch *Betula verrucosa*	3–4	*Bet v 1*[a]	Bet v 2[a]	Bet v 3 Bet v 4[a]	Bet v 6[b]	
Alder *Alnus glutinosa*	2–3	*Aln g 1*[c]		Aln g 4		
Hornbeam *Carpinus betulus*	4–5	*Car b 1*				
Hop-hornbeam *Ostrya carpinifolia*	4–5	*Ost c 1*				
Hazelnut *Corylus avellana*	2–3	*Cor a 1*[c]	Cor a 2		Cor a 6	
Beech *Fagus sylvatica*	4–5	*Fag s 1*				

Chestnut *Castanea sativa*	5–6	*Cas s 1*				
Oak *Quercus alba*	4–5	*Que a 1*				
London plane tree *Platanus acerifolia*	4–5					*Pla*
Olive *Olea europaea*	4–6		Ole e 2	Ole e 3 Ole e 8	Ole e 12[d]	
European ash *Fraxinus excelsior*	3–5					
Common privet *Ligustrum vulgare*	6–7					
Lilac *Syringa vulgare*	4–5			Syr v 3		
Mediterranean cypress *Cupressus sempervirens*	1–2					
Arizona cypress *Cupressus arizonica*	8–9					

Name	Season						
Japanese cypress *Chamaecyparis obtuse*	1–2						*Cha*
Japanese cedar *Cryptomeria japonica*	2–3						*Cry*
Mountain cedar *Juniperus ashei*	12–1						*Jun*

Weed Pollen

Name	Season						
Ragweed *Ambrosia artemisiifolia*	7–9			Amb a 8	Amb a 9 Amb a 10		
Mugwort *Artemisia vulgaris*	7–9	Art v 4	Art v 5			Art v 6	*Art 1*[a] Art v 3[a]
Feverfew *Parthenium hysterophorus*	7–9						Par h 1
Pellitory *Parietaria judaica*	All season	Par j 3	Par j 4				*Par j 1* *Par j 2*[a]
English plantain	4–9						*Pla l 1*[a]

Plantago lanceolata				
Goosefoot *Chenopodium album*	6–10	Che a 2	Che a 3	*Che a 1*[c]
Russian thistle *Salsola kali*	7–9	Sal k 4		Sal k 5 *Sal k 1*[a]
Amaranth *Amaranthus retroflexus*	7–9	Ama r 2		
Annual mercury *Mercurialis annua*	5–10	*Mer a 1*[c]		

Major allergens highlighted in italics.

[a]Commercially available for single- and multiplex analysis.

[b]Commercially available for singleplex only.

[c]Commercially available for multiplex analysis only.

[d]Allergen not officially acknowledged by the WHO/IUIS allergen nomenclature sub-committee.

[e]Sequence homology to N-terminus of Ole e 9, listed as carbohydrate-binding molecule.

From Pablos I, Wildner S, Asam C, et al. Pollen allergens for molecular diagnosis. *Curr Allergy Asthma Rep*. 2016;16:31.

The Anderson sampler is another suction device, but it is unique in its adaptability for enumerating viable fungal spores. Air passes through a series of sieve-like plates (either two or six), each containing 400 holes. Although the air moves from plate to plate, the diameter of the holes decreases. The larger particles are retained by the upper plates and the smaller ones by successive lower plates. A petri dish containing growth medium is placed beneath each sieve plate, and the spores that pass through the holes fall onto the agar and form

colonies. This method has value for identifying fungi whose spore morphologic features do not permit microscopic identification. In general, however, nonviable volumetric collection techniques more accurately reflect the actual spore prevalence than do volumetric culture methods. The volume of air sampled is easy to calculate for suction devices because the vacuum pumps may be calibrated. In the case of rotation impaction samplers, there are formulas that depend on the surface area of the exposed bar of slide, the rate of revolution, and the exposure time. After the adherent particles are stained and counted, their numbers can be expressed as particles per cubic meter of air. Gravitational samplers cannot be quantified volumetrically.

Fungal Culture

Fungi also may be studied by culture techniques. This is often necessary because many spores are not morphologically distinct enough for microscopic identification. In such cases, characteristics of the fungal colonies are required. Most commonly, petri dishes with appropriate nutrient agar are exposed to the air at a sampling station for 5 to 30 minutes. The plates are incubated at room temperature for about 5 days, and then inspected grossly and microscopically for the numbers and types of colonies present. Cotton-blue is a satisfactory stain for fungal morphologic identification. Potato-dextrose agar supports growth of most allergenic fungi, and rose bengal may be added to retard bacterial growth and limit the spread of fungal colonies. Specialized media such as Czapek agar may be used to look for particular organisms (e.g., *Aspergillus* or *Penicillium*).

The chief disadvantage of the culture plate method is a gross underestimation of the spore count. This may be offset by using a suction device such as the Anderson or Burkard sampler. A microconidium containing many spores still grows only one colony. There may be mutual inhibition or massive overgrowth of a single colony such as with *Rhizopus nigricans*. Other disadvantages are short sampling times, as well as the fact that some fungi (rusts and smuts) do not grow on ordinary nutrient media. Furthermore, avoiding massive spore contamination of the laboratory is difficult without precautions such as an isolation chamber and ventilation hood.

Immunologic Methods

Numerous immunologic methods of identifying and quantifying airborne allergens have been developed. In general, these methods require more sophisticated instruments and thus are unlikely to replace the physical pollen count. The immunologic assays do not depend on the morphologic features of the material sampled, but on the ability of eluates of this material collected on

filters to interact in immunoassays with human IgE or IgG or with mouse monoclonal antibodies (9,10). Studies at the Mayo Clinic have used a high-volume air sampler that retains 95% of particles larger than 0.3 µm on a fiberglass filter. The antigens, of unknown composition, are eluted from the filter sheet by descending chromatography. The eluate is dialyzed, lyophilized, and reconstituted as needed. This material is analyzed by RAST inhibition for specific allergenic activity or, in the case of antigens that may be involved in hypersensitivity pneumonitis, by interaction with IgG antibodies. The method is extremely sensitive. An eluate equivalent to 0.1 mg of pollen produced 40% to 50% inhibition in the short ragweed RAST. An equivalent amount of 24 µg of short ragweed pollen produced over 40% inhibition in the *Amb a 1* RAST (11). The allergens identified using this method have correlated with morphologic studies of pollen and fungal spores using traditional methods and with patient symptom scores. The eluates also have produced positive results on skin prick tests in sensitive human subjects (12). These techniques demonstrate that with short ragweed, different sized particles from ragweed plant debris can act as a source of allergen in the air before and after the ragweed pollen season. Unexpectedly, appreciable ragweed allergenic activity has been associated with particles <1 µm in diameter (13).

Use of low-volume air samples that do not disturb the air and development of a sensitive two-site monoclonal antibody immunoassay for the major cat allergen (*Fel d 1*) have made accurate measurements of airborne cat allergen possible (10). These studies confirm that a high proportion of *Fel d 1* is carried on particles <2.5 μm in diameter. During house cleaning, the amount of the small allergen-containing particles in the air approached that produced by a nebulizer for bronchial provocation (40 ng/m^3). The results indicate that significant airborne *Fel d 1* is associated with small particles that remain airborne for long periods. This is in contrast to prior studies with house dust mites (14) in which the major house dust mite allergen *Der p 1* was collected on large particles with diameters >10 μm. Little of this allergen remained airborne when the room was undisturbed.

Many pollen grains may be difficult to distinguish morphologically by normal light microscopic study. Immunochemical methods may permit such distinctions. Grass pollen grains collected from a Burkard trap were blotted onto nitrocellulose; then, by using specific antisera to Bermuda grass, a second antibody with a fluorescent label, and a fluorescent microscope study, Bermuda grass pollen grains could be distinguished from grass pollens of other species (15). These newer methods show promise because they measure allergenic materials that react with human IgE. Currently, immunochemical assays to quantify the major house dust mite allergens *Der p 1* and *Der f 1* and the major cat allergen *Fel d 1* in settled dust samples are commercially available. Real-time PCR-based approach has also been shown to be helpful in the identification and quantification of pollen taxa when analyzing pollen mixes, and can ultimately lead to the usage of multiplex real-time PCR for the simultaneous detection of different pollen and usage of high-throughput molecular methods (16).

■ STANDARDIZATION OF ALLERGENIC EXTRACTS

The need to standardize allergenic extracts has been recognized for many years. Variability in antigen composition and concentration is a major problem in both allergy testing and allergen immunotherapy. Without standardization of extracts, there is no accurate system of quality control. The clinician often is forced to alter immunotherapy schedules with each new vial of extract because of variability between different lots. Each allergen extract supplier uses his or her

own assays and rarely compares specific antigen concentrations with competitors. The result of this disparity is that the clinician must bring more art than science to the field of allergen immunotherapy. Fortunately, this is changing, with the requirement for standardization of ragweed pollen, house dust mite, cat dander, grass pollen extracts, and venom proteins. Currently, standardized allergen extracts licensed for distribution in the United States include cat hair, cat pelt, dust mites (*Dermatophagoides farinae and pteronyssinus*), Bermuda grass, Kentucky (june) bluegrass, meadow fescue grass, orchard grass, redtop grass, perennial ryegrass, sweet vernal grass, timothy grass, short ragweed, honey-bee venom, wasp venom, white-faced hornet venom, yellow-faced hornet venom, yellow-jacket venom, and mixed vespid venom. The development of purified and even cloned allergens that can be expressed in bacteria or yeast hosts have allowed the production of vast quantities of allergen extract with little or no variance between batches (17). With investigators, clinicians, and government agencies that license extracts demanding improved standardization, it is expected that more progress in this area of allergy will be made in the near future.

Quantification of Allergens

The traditional method of preparing and labeling allergens for clinical use is to extract a known weight of defatted pollen or other allergenic particle in a specified volume of fluid. For example, 1 g in 100 mL of fluid would yield a 1% (1:100) solution. This weight per volume (w/v) system still is one of the most commonly used in clinical practice. This solution can be concentrated or diluted as needed.

Another system of measurement, used by some extract manufacturers, is the protein-nitrogen unit (PNU). The basis of the PNU system is the fact that most allergenic moieties of pollens are proteins, and that the ratio of protein to dry weight of pollen varies from plant to plant. In this method, nitrogen is precipitated by phosphotungstic acid and measured by the micro-Kjeldahl technique. One PNU is 0.0l μg of protein nitrogen. Both of these methods are used for nonstandardized inhalant and food allergens; clinicians generally must communicate in terms of these measurements. Unfortunately, neither the w/v nor the PNU truly measures allergenic activity, because not all measured proteins and extractable components in the solution are allergenic. In addition, many complex allergens are destroyed during the harsh extraction procedure. Such problems have been circumvented through the use of biologic assays of "functional" allergen reactivity. Currently, ragweed pollen, grass pollen, house

dust mite, and cat allergen extracts are standardized, and their activity is expressed in allergen units or bioequivalent allergy units. Some extracts, grass pollen in particular, are standardized and prescribed using the BAU (bioequivalent allergy unit), which is based on intradermal skin testing. A threefold dilution is calculated to induce a sum of erythema of 50 mm (D50). The allergen extract with a D50 of the 14th dilution is arbitrarily assigned a value of 100,000 BAU/mL. In addition to grass, cat and dust mite are labeled similarly; ragweed is labeled as *Amb a* 1 units, and venoms are microgram protein based on hyaluronidase and phospholipase activity (18,19).

Other allergen extracts may be added to this list in the future. It is essential for anyone devising immunotherapy regimens to have an appreciation for the biologic assays of allergenicity, which are described later.

■ CHARACTERIZATION OF ALLERGENS

Although numerous methods are available to characterize an allergen, many of these, such as the determination of protein content, molecular weight, and isoelectric point, are not unique to the study of allergenic compounds. These are simply methods of describing any protein. Several categories of tests, however, are restricted to studying molecules responsible for IgE-mediated symptoms.

Radioallergosorbent Test

The RAST is described elsewhere in this text. Although primarily used in the quantification of antigen-specific IgE, the test may be adapted to determine antigen concentrations. To measure potency, the unknown allergen is immobilized onto solid-phase supports (cellulose disks or beads) and reacted with a known quantity of antigen-specific IgE in a standard test system. For comparison, the extracts are compared with a reference standard, which should be carefully chosen. The quantity of extract required to obtain a specified degree of reactivity is determined. The greater the binding of IgE to the antigen, the greater the allergenicity.

RAST Inhibition Assay

The most widely used assay for *in vitro* potency of allergenic extract is the RAST inhibition method. This test is a variation of the direct RAST. Serum from an allergic individual (containing IgE) is first mixed with the soluble unknown allergen. Next, a standard amount of the solid-phase (immobilized) allergen is added. The more potent the fluid phase allergen, the less IgE is free to bind to the

solid-phase allergen. The technique and its statistical analysis have been standardized. RAST inhibition usually is the key technique to assess total allergenic activity of an extract and is used by manufacturers to calibrate new batches by comparison with the in-house reference preparation. Some have raised concern regarding the continued use of RAST inhibition as a standard technique. The arguments concern the fact that the choice of antigen for the solid-phase reaction is variable and may influence results. In addition, the finite supply of allergenic reference sera limits reproducibility: without identical reference sera and immobilized allergen, comparisons are impossible. Further development of monoclonally derived IgE and recombinant allergens may help with these concerns.

Assessment of Allergenicity

Biochemical methods for analyzing allergens, such as protein composition and concentration, are practical but may impart little about the allergenicity of the extract. Immunologic reactivity with IgE antibodies as assessed *in vitro* and *in vivo* provides this information. Preparations of inhalant allergens contain more than one antigen. Of the several antigens in a mixture, usually one or more dominate in both frequency and intensity of skin reactions in sensitive persons. It is inferred from this that these antigens are the most important clinically. Not all persons allergic to a certain pollen allergen react to the same antigens from that pollen allergen extract, however. The antigens of tree, grass, and weed pollens are immunologically distinct, and this agrees with the clinical and skin test data. As more allergens are isolated and purified, correlations between immunogenicity and biochemical structure have emerged.

There are two methods of determining the allergenicity of an individual protein. One method is to look at how many people make an IgE response against a certain allergen. A major allergen has been defined as one that binds IgE in 50% or more of sensitized patients (2,20). A second method of determining the allergenicity of a protein is to determine how much of the IgE is bound to that protein. For example, in experiments involving the major cat allergen, *Fel d 1*, it has been reported that 90% of the IgE antibodies against cat are reacting against *Fel d 1* (1).

Theories of Allergenicity

What characteristics determine whether a particle or a protein can become an important allergen? For a particle to be clinically significant as an aeroallergen, it must be buoyant, present in significant numbers, and allergenic. In general, the

insect-pollinated (entomophilous) plants produce more sticky and heavy pollen that do not become airborne, as opposed to wind-pollinated (anemophilous) plants, which, by necessity, produce lighter particles that are far more buoyant and travel for greater distances. However, being present in high concentrations is not enough to dictate allergenicity. For example, pine pollen is abundant in certain regions and is buoyant, but because it does not readily elicit IgE antibodies, it is not a significant aeroallergen. The characteristics of allergenic particles have been examined and theories relating to their allergenicity are described subsequently.

Structural Properties of Aeroallergens

Some protein structures do seem to be more likely to be associated with allergenicity. One factor that may be important is the simultaneous exposure of multiple allergenic epitopes on a single structure to promote cross-linking of IgE. The major birch allergen, *Bet v 1*, has been compared to a naturally occurring, nonallergenic protein with significant sequence homology using three-dimensional computer modeling. The nonallergenic protein appears to have fewer epitopes on the exposed surface of the molecule and is more likely to be a monomer than *Bet v 1* (21). Computer models that predict allergenicity suggest that the presence of multiple allergenic motifs on a protein makes it more likely to be allergenic (22). There is also evidence from computer modeling of known allergen sequences that a number of diverse allergens have a common structural motif, a groove inside an α-β motif, which is also found in some toxins and defensins (23).

Do specific carbohydrate determinants promote allergenicity? Sera from allergic patients often have IgE that interacts with cross-reacting carbohydrate determinants. Many of these cross-reacting carbohydrate determinants are present in a wide variety of proteins and across very different species. There may be some *in vivo* effects of these epitopes on an immunologic level. However, cross-reacting carbohydrate epitopes often appear to be a source of positive serologic results without clinical significance (24). Carbohydrates have more recently been identified in IgE-mediated reactions whereby investigators at the University of Virginia discovered an IgE-based response to the carbohydrate antigen galactose-α-1,3-galactose (α-gal) as a cause for delayed anaphylactic reactions following ingestion of mammalian meat which contains this allergen in abundance (25).

It has been hypothesized that proteins might be more allergenic because of their structural similarity to invasive organisms. Helminths are classically

associated with high IgE levels and intuitively might be associated with allergy, but studies in animal models and human populations suggest that helminthic infection is generally protective against the development of allergies (26). An exception, the fish parasite *Anisakis*, is associated with allergenic symptoms during infection and has been reported as an occupational respiratory allergen in fish-processing factories (27).

Chemical Properties of Allergens and Immune Interactions

It has been known for some time that the major house dust mite allergen, *Der p 1*, has structural similarity to cysteine protease enzymes (28). The enzymatic activity of this allergen may have a role in the development of atopic sensitization and asthma. A series of experiments have been done in which mice are sensitized using enzymatically active or inactive *Der p 1* ultimately revealing that enzymatic activity of an allergen contributes to its allergenicity by eliciting an exaggerated inflammatory response in the lungs and increased total IgE levels (29–31).

Several mechanisms have been proposed to explain the relationship between enzymatic function and the development of sensitization. Enzymatically active *Der p 1* can disrupt tight junction between respiratory epithelia in cell cultures (32). This has been proposed as a mechanism by which the allergen can be delivered through the epithelium to the immune cells. Other dust mite allergens, *Der p* 3 (trypsin), 6 (chymotrypsin), and 9 (serine protease) have also been shown to disrupt the tight junctions in respiratory epithelium (33).

Several immunologic mechanisms have also been proposed to explain the apparent allergenic effects of dust mite enzymes. The enzymatic activity of *Der p 1* has been shown to cleave the low-affinity IgE receptor (FcεRII or CD23) from human B cells, which may augment IgE synthesis (34,35). It has also been shown that dendritic cells incubated with enzymatically active *Der p 1* generate less IL-12, which skews away from a T_H1 response to a T_H2 cell response (36).

Properties of Pollen Grains

It is important to remember that pollen grains are complex structures designed to deliver plant reproductive material. They have many chemicals and proteins that are presented to the respiratory mucosa at the same time as the most allergenic proteins. The biochemical properties of these pollen grains also contribute to their allergenicity. It has been shown that birch, grass, and ragweed pollens contain both serine proteases and cysteine proteases and that these proteases can also disrupt epithelial tight junctions (37). Type 1 grass pollen allergens appear

to migrate into the stratum corneum skin via the hair follicles as soon as 15 minutes. This has been proposed as a mechanism of sensitization in atopic dermatitis (38).

Pollen extracts also appear to have direct effects on the immune system. In cell culture, birch pollen extracts have been found to direct dendritic cells toward a more T_H2 type of antigen presentation and to recruit more T_H2 cells for antigen presentation (39). In a recent study, it was shown that urbanization and pollution correlated with a less diverse pollen-associated microbiome which in turn translates to altered allergenicity of the pollen because of environmental and microbial stress (40). Pollen allergen provocation has also been shown to induce ROS (reactive oxygen species) generation in patients with asthma and allergic rhinitis which in turn promotes allergic inflammation by altering dendritic cell function and causing a T_H1/T_H2 imbalance (41).

Effects of Particle Size

Aeroallergen particle size is an important element of allergic disease. Airborne pollens are in the range of 20 to 60 μm in diameter; mold spores usually vary between 3 and 30 μm in diameter or longest dimension; house dust mite particles are 1 to 10 μm. Protective mechanisms in the nasal mucosa and upper tracheobronchial passages remove most of the larger particles, so only those 3 μm or smaller in diameter are thought to reach the alveoli of the lungs. Hence, the conjunctivae and upper respiratory passages receive the largest dose of airborne allergens. Despite this conventional wisdom, examination of tracheobronchial aspirates and surgical lung specimens has revealed whole pollen grains in the lower respiratory tract (42). These are considerations in the pathogenesis of allergic rhinitis and bronchial asthma as well as the effects of chemical and particulate atmospheric pollutants.

The development of asthma after pollen exposure is enigmatic because pollen grains are thought to be deposited in the upper airways as a result of their large particle size. Experimental evidence suggests that rhinitis, but not asthma, is caused by inhalation of whole pollen in amounts encountered naturally (43). Asthma caused by bronchoprovocation with solutions of pollen extracts is easily achieved in the laboratory, however. Pollen asthma may be caused by the inhalation of pollen debris that is small enough to access the bronchial tree.

Ragweed asthma supports this hypothesis. The major ragweed allergen, *Amb a 1,* has been found in ambient air, even in the absence of whole pollen (12). Extracts of materials collected on an 8-μm filter that excludes ragweed pollen

grains still appear to contain ragweed allergen based on skin testing and ragweed-IgG inhibition (44).

In Melbourne and London, severe outbreaks of asthma have been reported during some thunderstorms. This phenomenon has been referred to as thunderstorm asthma. People who had asthma exacerbations during a thunderstorm were more likely to be sensitive to grass pollen (45). Grass pollen is generally considered to be too large to access the smaller airways of the lungs. However, exposure of grass pollen grains to water creates rupture into smaller, respirable-size starch granules with intact allergens (46). These starch granules have been found to increase 50-fold during a rainstorm, and thunderstorm asthma patients are more likely to be sensitive to the starch granules than other asthma patients (45,47). There is evidence for a similar effect of *Alternaria* spores. Thunderstorm asthma patients were more likely to be sensitive to *Alternaria,* and counts of broken *Alternaria* spores correlate with hospital admissions during a thunderstorm (48).

POLLEN ALLERGENS

Pollen grains are living male gametophytes of higher plants (gymnosperms and angiosperms). Each grain has an internal limiting cellulose membrane, the intine, and a two-layered external covering, the exine, composed of a durable substance called sporopollenin. Sporopollenin is primarily a high molecular weight polymer of fatty acids.

Morphologic studies of pollens using the scanning electron microscope disclose an intricate infrastructure. The morphologic structure varies in relation to size, number of furrows, form and location of pores, thickness of the exine, and other features of the cell wall (spines, reticulations, an operculum in grass pollens, and air sacs [bladders] in certain conifers). Ragweed pollen is about 20 μm in diameter, tree pollens vary from 20 to 60 μm, and grass pollens, which are all morphologically similar, are usually 30 to 40 μm. The identification of pollens important in allergic disease is not difficult and is certainly within the capabilities of the physician with no special expertise in botany (49,50).

Some plants produce prodigious amounts of pollen. A single ragweed plant may expel 1 million pollen grains in a single day. Trees, especially conifers, may release so much pollen that it is visible as a cloud and may be scooped up by the handful after settling. The seasonal onset of pollination of certain plants (e.g., ragweed) is determined by the duration of light received daily. Pollination occurs earlier in the northern latitudes and demonstrates little year-to-year variation in

terms of date. In the belt from the central Atlantic to the north-central states, August 15 is a highly predictable date for the onset of ragweed pollination. Most ragweed pollen is released between 6:00 AM and 8:00 AM, and release is enhanced by high temperature and humidity. Extended dry spells in early summer inhibit flower development, reduce ragweed pollen production, and thus result in lower counts in August and September.

Most brightly colored flowering plants are of little clinical importance in inhalant allergy because their pollen generally is entomophilous rather than anemophilous. Roses and goldenrod are examples of plants that often are erroneously thought to cause pollinosis because of the time they bloom. Nevertheless, in isolated cases, the pollens of most entomophilous plants can sensitize and then cause symptoms if exposure is sufficient. Of the pollens of anemophilous plants, ragweed has a long range, having been detected 400 miles out at sea. The range of tree pollens is much shorter. Thus, an individual living in the center of a city is more likely to be affected by weed and grass pollens than by trees. Local weed eradication programs, more often legislated than accomplished, are futile in light of the forgoing information. Air conditioners significantly reduce indoor particle recovery because windows are shut when they operate and they largely exclude outdoor air. Numerous online resources are available to provide up-to-date information regarding allergenic molecules and pollens, and www.allergome.com, collaborating with the University of Queensland, is one that is used frequently and widely cited in the scientific literature.

CLASSIFICATION OF ALLERGENIC PLANTS

The botanical considerations and taxonomic scheme given here are not exhaustive (49,50). Individual plants, their common and botanical names, geographic distributions, and relative importance in allergy are reviewed in Chapter 7.

Anatomy

Seed-bearing plants produce their reproductive structures in cones or flowers. Gymnosperms ("naked seeds"; class Gymnospermae) are trees and shrubs that bear their seeds in cones. Pines, firs, junipers, spruces, yews, hemlocks, savins, cedars, larches, cypresses, retinisporas, and ginkgoes are gymnosperms. Angiosperms produce seeds enclosed in the female reproductive structures of the flower. Angiosperms may be monocotyledons, whose seeds contain one "seed leaf" (cotyledon), or dicotyledons, with two seed leaves. Leaves of

monocotyledons have parallel veins, whereas leaves of dicotyledons have branching veins. Grasses are monocotyledons; most other allergenic plants are dicotyledons.

The flower has four fundamental parts:

1. *Pistils* (one or more) are the female portion of the plant and consist of an ovary at the base, a style projecting upward, and a stigma, the sticky portion to which pollen grains adhere.

2. *Stamens*, which are the male portions of the plant, are variable in number and consist of anthers borne on filaments. Pollen grains are produced in the anthers.

3. *Petals*, the colored parts of the flower, vary from three to many in number.

4. *Sepals*, the protective portion of the flower bud, are usually green and three to six in number.

The phylogenetically primitive flower had numerous separate parts, as typified by the magnolia. Fusion of flower parts and reduction of their number is a characteristic of phylogenetic advancement. As a group, dicotyledons are more primitive than monocotyledons.

A "perfect" flower contains both male and female organs; an "imperfect" flower contains only stamens or only pistils. Monoecious ("one house") plants bear both stamens and pistils; the individual flowers may be perfect or imperfect. Dioecious ("two houses") plants have imperfect flowers, and all flowers on a particular plant are the same type (male and female). Ragweed is a monoecious plant with perfect flowers; corn is a monoecious plant with imperfect flowers; willows are dioecious plants. Like the flowering plants, gymnosperms may be either monoecious (pines) or dioecious (cypresses and ginkgoes).

Taxonomy

Plants are classified in a hierarchical system. The principal ranks, their endings, and some examples are as follows:

Class (-ae): Angiospermae, Gymnospermae

Subclass (-ae): Monocotyledonae, Dicotyledonae

Order (-ales): Coniferales, Salicales

Suborder (-ineae)

Family (-aceae): Asteraceae, Poaceae

Subfamily (-oideae)

Tribe (-eae)

Genus (no characteristic ending; italicized): *Acer*

Species (genus name plus "specific epithet"): *Acer rubrum*

Trees: Gymnosperms

Trees may be gymnosperms or angiosperms. The gymnosperms include two orders, the Pinales formerly known as coniferales (conifers) and the Ginkgoales. The Pinales consist of seven families: Araucariaceae, Cephalotaxaceae, Pinaceae, Podocarpaceae, Sciadopityaceae, Taxaceae, and Cupressaceae. Only certain genera within these families produce clinically significant allergens as established by the IUIS (51).

Conifers grow mainly in warmer temperate climates, though they are found anywhere from the northern latitudes in the arctic to the southern hemisphere. They have needle-shaped leaves. The following three families belong to the Pinales/coniferales and are germane to this discussion.

Pinaceae (Pines, Spruces, Firs, and Hemlocks)

Pines are monoecious evergreens whose leaves are arranged in bundles of two to five and are enclosed at the base by a sheath (all other members of the Pinaceae family bear leaves singly, not in bundles). The pollen grains of pines are 45 to 65 μm in diameter and have two bladders (Fig. 6.2). This pollen occasionally has been implicated in allergy. Spruces produce pollen grains morphologically similar to pine pollen but much larger, ranging from 70 to 90 μm exclusive of the bladders. Hemlock pollen grains may have bladders, depending on the species. The firs produce even larger pollen grains, ranging from 80 to 100 μm, not including the two bladders.

Cupressiaceae (Junipers, Cypresses, Cedars, and Savins)

Most of these trees are dioecious and produce large quantities of round pollen grains 20 to 30 μm in diameter with a thick intine (internal membrane). The Mediterranean cypress and its American counterpart, the Arizona Cypress, are important sources of pollen allergens contributing to anywhere from 2.4% to 35.4% sensitization rates and up to 42.7% in Italy (52–54). The major allergens *Cup a 1* and *Cup s 1* have high sequence homology and are allergenic pectate lyases. Similarly, allergenic pectate lyases have been acknowledged as major allergens in mountain cedar (*Jun a 1*) as well as in the Japanese cypress (*Cho o 1*) and Japanese cedar (*Cry j 1*). These allergens cause locally high sensitization

rates and are an important cause of allergic rhinitis ("cedar fever") in certain parts of Texas (*Jun a 1*) and Japan (*Cho o 1 and Cry j 1*) and have/proliferated where the ecosystem has been disturbed by overgrazing of the grasslands (54,55).
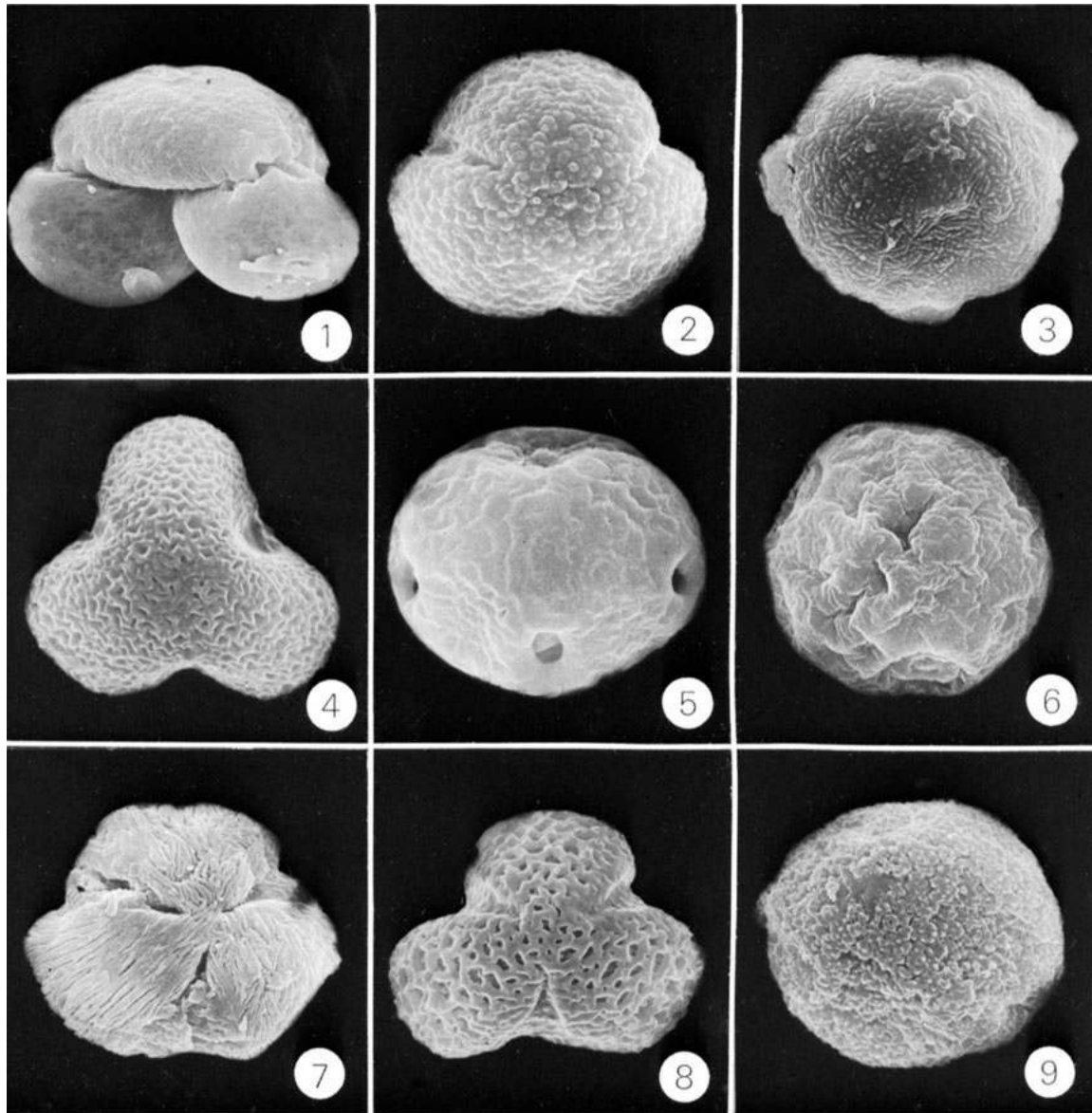
■ **FIGURE 6.2** Scanning electron photomicrographs of early spring airborne hay fever–producing pollen grains: *1,* pine (*Pinus*); *2,* oak (*Quercus*); *3,* birch (*Betula*); *4,* sycamore (*Platanus*); *5,* elm (*Ulmus*); *6,* hackberry (*Celtis*); *7,* maple (*Acer*); *8,* willow (*Salix*); *9,* poplar (*Populus*). (Courtesy of Professor James W. Walker.)

Taxodiaceae (Bald Cypress and Redwood)

Bald cypress have scale or needle-like leaves with pollen grains that are spheroidal, ranging 25 to 36 μm in diameter, and possess a single aperture. They

grow in moist swamps or wetlands and may be a minor cause of allergic rhinitis in Florida. The redwood is typically found in southern Oregon and California and has small evergreen needle-like leaves with pollen grains that are also spheroidal, 1-aperturate, and range 25 to 36 μm in diameter; it is an uncommon cause of allergic rhinitis.

Trees: Angiosperms

Most allergenic trees are in this group. The more important orders and families are listed here with relevant notations. Other trees have been implicated in pollen allergy, but most of the pollinosis in the United States can be attributed to those mentioned here.

Order Salicales, Family Salicaceae (Willows and Poplars)

Willows are entomophilous, dioecious trees, and have pollen grains that are prolate (i.e., elongated spheroid) and subprolate and ranging in size from 28 to 34 μm. While they are not generally considered allergenic, they can produce strong skin test responses in individuals (Fig. 6.2). Poplars, however, are wind pollinated, and some (e.g., species of *Populus*) are of considerable allergenic importance in the Great Lakes and Rocky Mountain region. Poplar pollen grains are either spherical or prolate or subprolate, 25 to 40 μm in diameter, and characterized by a thick intine (Fig. 6.2). The genus *Populus* includes poplars, aspens, and cottonwoods. Their seeds are borne on buoyant cotton-like tufts that may fill the air in June like a localized snowstorm. Patients often attribute their symptoms to this "cottonwood," but the true cause usually is grass pollens, and this release occurs after the tree has been pollinated.

Order Betulales, Family Betulaceae (Birches)

Betula species are widely distributed in North America and produce abundant pollen that is highly allergenic. The pollen grains are 20 to 30 μm and suboblate to oblate (flattened at the poles), generally with three pores, although some species have as many as seven (Figs. 6.2 and 6.3). The pistillate catkins may persist into winter, discharging small winged seeds. Birch pollen sensitivity is also significant source of cross-reactivity to a myriad of fresh fruits, vegetables, and tree nuts resulting in symptoms of pollen-food syndrome (PFS) (56).
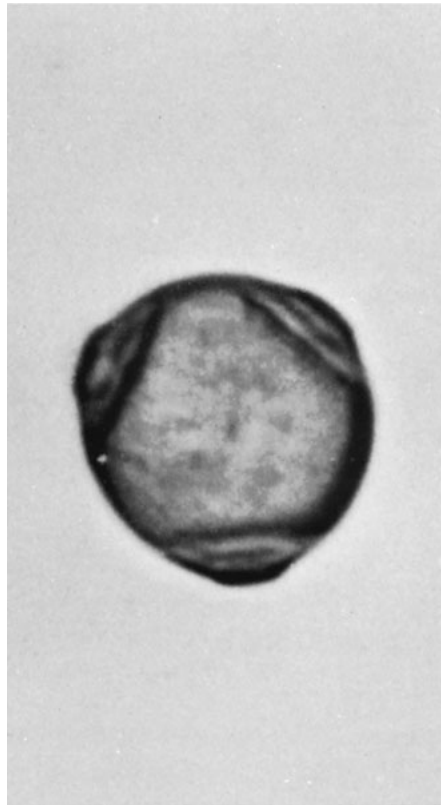
■ FIGURE 6.3 Birch (*Betula nigra*). Average diameter is 24.5 μm. Pollen grains have three pores and a smooth exine. (Courtesy of Center Laboratories, Port Washington, NY.)

Order Fagales, Family Fagaceae (Beeches, Oaks, Chestnuts, and Chinquapins)

Of the six to eight genera that comprises Fagaceae, five are found in North America, of which only the beeches (*Fagus*) and oaks (*Quercus*) are wind pollinated and of allergenic importance. The pollens of these two genera are morphologically similar but not identical. They are prolate subspheroidal or suboblate, 40 μm in diameter, with an irregular exine (outer covering) and three tapering furrows (Figs. 6.2 and 6.4). Both produce abundant pollen; oaks in particular cause a great deal of tree pollinosis in areas where they are numerous. American chestnuts are entomophilous and are generally not associated with allergic rhinitis.

Order Urticales, Family Ulmaceae (Elms and Hackberries)

About 20 species of elms are in the Northern Hemisphere, mainly distributed east of the Rocky Mountains. They are anemophilous, produce large amounts of allergenic pollen, and continue to be a major cause of tree pollinosis despite the almost total elimination of the American elm by Dutch elm disease. Elm pollen are suboblate to spheroidal, range in diameter from 35 to 40 μm, and have four to six pores with a thick, rippled exine (Fig. 6.2). Hackberries are unimportant

for this discussion.
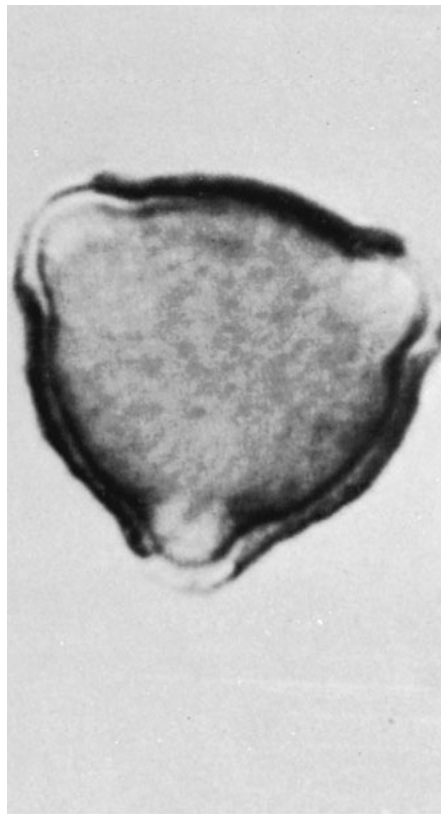
■ **FIGURE 6.4** Oak (*Quercus* species). Average diameter is 32 μm. Pollens of the various species are similar, with three long furrows and a convex, bulging, granular exine. (Courtesy of Center Laboratories, Port Washington, NY.)

Order Juglandales, Family Juglandaceae (Walnuts)

Walnut trees (*Juglans*) are generally an infrequent cause of pollinosis, though can be bothersome in Oregon, California, and northeastern United States. The pollen grains are isopolar, heteropolar, or paraisopolar, range 30 to 40 μm in diameter, and have about 12 pores predominantly localized in one area and a smooth exine (Fig. 6.5).

The Hickories (Carya)

These anemophilous trees produce large amounts of highly allergenic pollen in eastern and central United States. Pecan trees, a species within this genus, in particular, are important in the etiology of allergic rhinitis where they grow or are cultivated. The pollen grains are isopolar, heteropolar, or paraisopolar, 40 to 50 μm in diameter, possess a thick intine, and usually contain three or four germinal pores.

Order Myricales, Family Myricaceae (Bayberries)

Bayberries used to belong in the genus Myrica (currently under the genus

Morella) and produce windborne pollen closely resembling the pollen of the *Betulaceae*. They produce a wax which is used to scent candles and perfume. The wax myrtles are thought to cause pollinosis in some areas of Florida and southeastern United States.
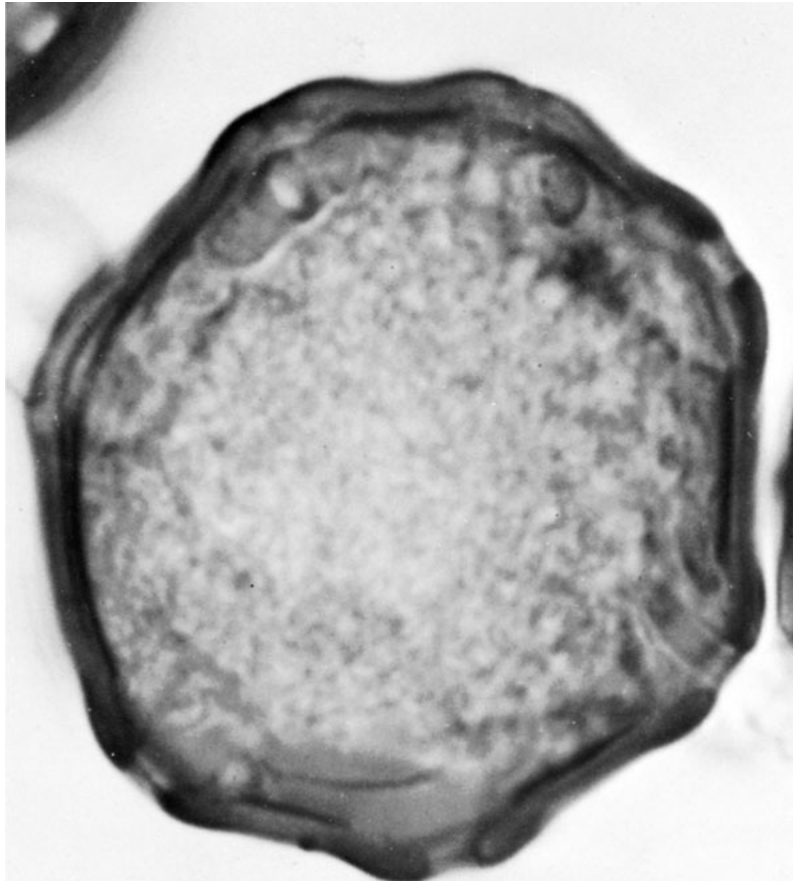
■ **FIGURE 6.5** Walnut (*Juglans nigra*). Average diameter is 36 μm. Grains have multiple pores surrounded by thick collars arranged in a nonequatorial band. (Courtesy of William P. Solomon, MD, University of Michigan, Ann Arbor, MI.)

Order Urticales, Family Moraceae (Mulberries)

Certain members of the approximately 40 genera *Morus* grow in large numbers as shrubs and may be highly allergic. The pollen grains are spheroidal, about 17 to 21 μm in diameter, and contain two or three germinal pores arranged with no geometric pattern (neither polar nor meridial).

Order Hamamelidales, Family Platanaceae (Sycamores)

These anemophilous trees are sometimes called "plane trees" and often planted in streets to provide shade. The grains of their plentiful pollen are oblate to suboblate, about 20 μm in diameter, and without pores. There are three or four furrows on the thin, granular exine (Fig. 6.2). Regionally, sycamores may be of

allergenic significance.

Order Rutales, Family Simaroubaceae (Ailanthus)

Only the tree of heaven (*Ailanthus altissima*) is of allergenic importance regionally. Its pollen grains are prolate to subprolate, have a diameter of about 25 μm and are characterized by three germinal furrows and three germinal pores. It is native to China and has been naturalized in much of the United States.

Order Malvales, Family Malvaceae (Lindens)

One genus, *Tilia* (the linden or basswood tree), is of allergenic importance, although it is insect pollinated. The pollen grains are paraisopolar to peroblate, 28 to 36 μm in diameter, tri-colporate, with germ pores sunk in furrows in a thick, reticulate exine and intine.

Order Sapindales, Family Aceraceae (Maples)

There are more than 100 species of maple, of which 13 are native to the United States and are important in allergy. These anemophilous trees have pollen grains that are prolate to spheroidal with usually three furrows or three pores (Fig. 6.2). Box elder, a species of *Acer,* is particularly important because of its wide distribution, its prevalence, the amount of pollen it sheds, and has a distinct rugulate-undulating sexine.

Order Oleales, Family Oleaceae (Ashes)

This family contains about 65 species, many of which are prominent among the allergenic trees found in the eastern and southeastern United States. Pollen grains are prolate or suboblate to spheroidal, have a diameter of 20 to 25 μm, and usually have three to six furrows (Fig. 6.6). The exine is coarsely reticulate.

Grasses (Poaceae)

Grasses are monocotyledons of the family Poaceae (or Gramineae). There are about 600 genera and 10,000 species of grasses worldwide with the majority of the allergenic species belonging to the subfamilies of Pooideae, Chloridoideae, and Panicoideae. The flowers usually are perfect (Figs. 6.7 and 6.8). Pollen grains of most allergenic grasses are spheroidal or ovoidal, 20 to 25 μm in diameter, with one germinal pore or furrow and a thick intine (Fig. 6.9). Some grasses are self-pollinated and therefore noncontributory to allergies. The others are wind-pollinated, but of the more than 1,000 species in North America, only a few are significant in producing allergic symptoms. Those few, however, are important in terms of the numbers of patients affected and the high degree of morbidity produced. Most of the allergenic grasses are cultivated and therefore

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are prevalent where people live.

The grass family contains several subfamilies and genus of varying importance to allergists. The most important are listed here. As with trees, grass pollen also results in cross-reactivity to a variety of fresh fruits and vegetables contributing to the phenomenon of PFS.
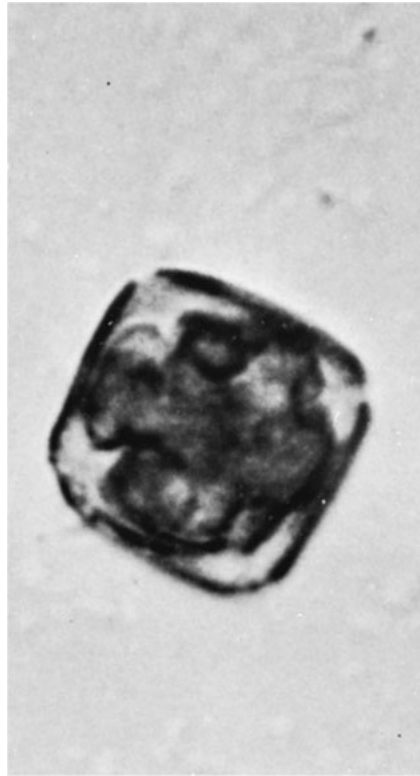
■ **FIGURE 6.6** Ash (*Fraxinus americana*). Average diameter is 27 μm. The pollen grains are square or rectangular with four furrows. (Courtesy of Center Laboratories, Port Washington, NY.)

■ FIGURE 6.7 Timothy grass (*Phleum pratense*). Morphologic features of the flowering head. (Courtesy of Arnold A. Gutman, MD, Associated Allergists Ltd., Chicago, IL.)

FIGURE 6.8 June grass or bluegrass (*Poa pratensis*). Morphologic features of the flowering head. (Courtesy of Arnold A. Gutman, MD, Associated Allergists Ltd., Chicago, IL.)
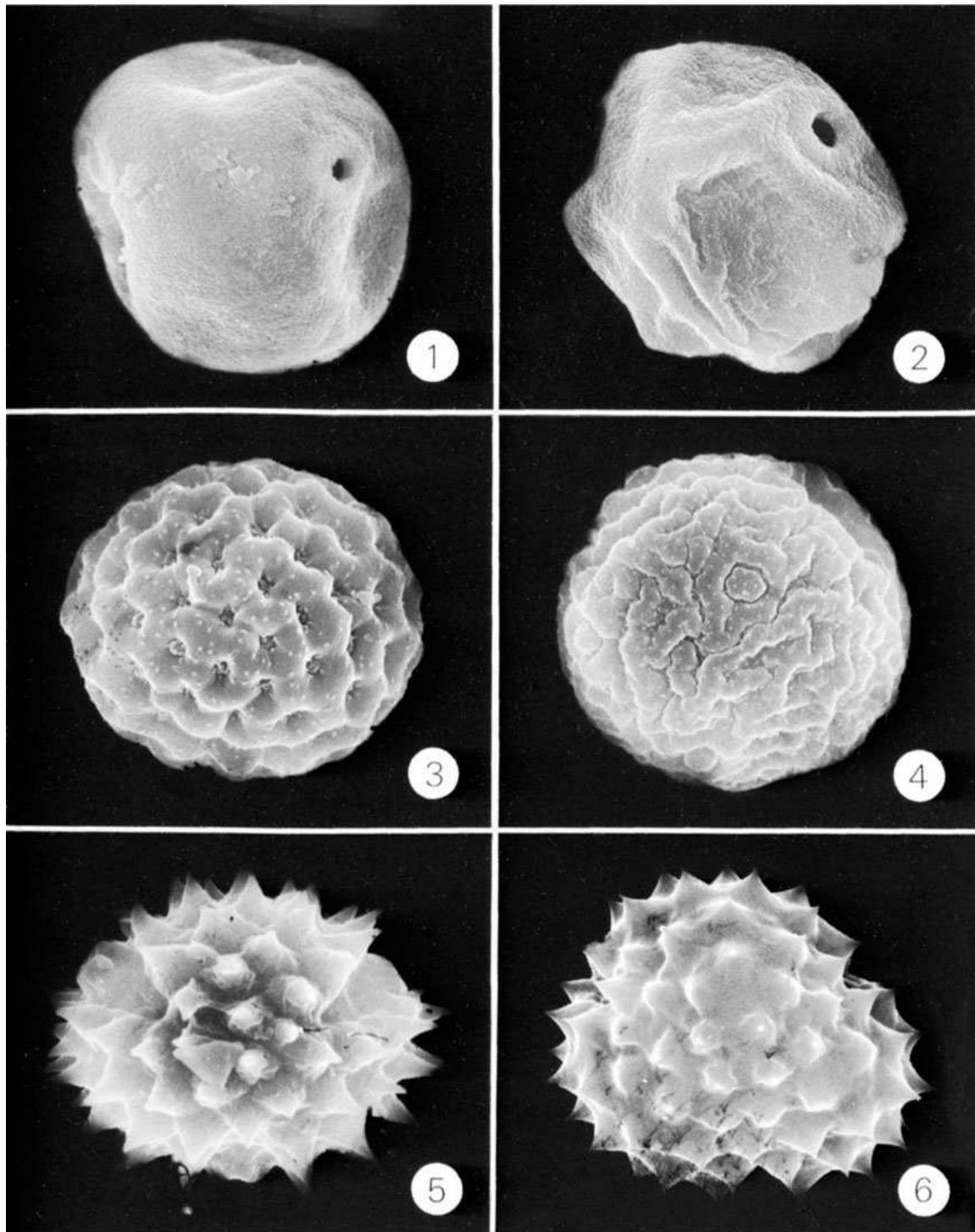
■ **FIGURE 6.9** Early and late summer airborne hay fever–producing pollen grains: *1,* timothy (*Phleum*); *2,* orchard grass (*Dactylis*); *3,* lamb's quarters (*Chenopodium*); *4,* plantain (*Plantago*); *5,* goldenrod (*Solidago*); *6,* ragweed (*Ambrosia*). (Courtesy of Professor James W. Walker.)

Subfamily Pooideae

The subfamily Pooideae consists of orchard grass (*Dactylis glomerata*), meadow fescue grass (*Festuca pratensis*), perennial rye (*Lolium perenne*), Kentucky

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bluegrass (*Poa pratensis*), timothy grass (*Phleum pratense*), sweet vernal grass (*Anthoxanthum odoratum*), and redtop/bent grass (*Agrostis gigantea*) and are typically found in the temperate regions of North America (Figs. 6.8 and 6.9). Timothy and redtop are cultivated as forage, and timothy is used to make hay. Other species of *Agrostis* immunologically similar to redtop are used for golf course greens. Timothy pollens are 30 to 35 μm in diameter. Redtop pollens are 25 to 30 μm. Sweet vernal grass (*Anthoxanthum odoratum*) is an important cause of allergic rhinitis in areas where it is indigenous. In the total picture of grass allergy, however, it is not as important as the species previously mentioned. The pollen grains are 38 to 45 μm in diameter.

Subfamily Chloridoideae

Bermuda grass (*Cynodon dactylon*) is abundant in all the southern states. It is cultivated for decorative and forage purposes. It sheds pollen almost year round and is a major cause of pollen allergy. The pollen grains are 35 μm in diameter.

Subfamily Panicoideae

The subfamily Panicoideae consists of bahia grass (*Paspalum*) and Johnson grass (*Sorghum*) and often found in moist, tropical to subtropical zones. These species are important in containing erosion in the gulf-shore states and serve as forage for livestock.

Weeds

A weed is a plant that grows where people do not intend it to grow. Thus, a rose could be considered a weed if it is growing in a wheat field. What are commonly called weeds are small annual plants that grow without cultivation and have no agricultural or ornamental value. All are angiosperms and most are dicotyledons. Those of interest to allergists are wind pollinated, and thus tend to have relatively inconspicuous flowers.

Family Asteraceae (Compositae)

The composite family is perhaps the most important allergenic weed group. Sometimes called the sunflower family, it is characterized by multiple tiny flowers arranged on a common receptacle and usually surrounded by a ring of colorful bracts. There are many tribes within this family; only those of allergenic or general interest are mentioned.

Tribe Heliantheae includes sunflower, dahlia, zinnia, and black-eyed Susan. Most heliantheae are herbs or shrubs and cause pollinosis mainly among those who handle them.

FIGURE 6.10 Giant ragweed (*Ambrosia trifida*). Arrangement of staminate heads. (Courtesy of Arnold A. Gutman, MD, Associated Allergists Ltd., Chicago, IL.)

Tribe Ambrosieae, or the ragweed tribe, shed enormous amount of pollen and is the most important cause of allergic rhinitis and allergic asthma in North America. Other common weeds in this tribe are the cocklebur and marsh elder. *Ambrosia trifida*, giant ragweed, may grow to a height of 4.5 m (15 ft) (Fig. 6.10). The leaves are broad with three to five lobes. The staminate heads are borne on long terminal spikes, and the pistillate heads are borne in clusters at the base of the staminate spikes. The pollen grains are spheroidal, 16 to 19 μm in diameter, and are slightly smaller than those of *Ambrosia artemisiifolia*, short ragweed. Short ragweed grows to a height of 120 cm (4 ft) (Fig. 6.11). Its leaves are more slender and usually have two pinnae on each side of a central axis. Pollen grains range from 17.5 to 19.2 μm in diameter and are almost indistinguishable from those of giant ragweed (Figs. 6.9, 6.12, and 6.13). There is no practical reason, however, for distinguishing between the two. *Ambrosia bidentata*, southern ragweed, is an annual that grows from 30 to 90 cm (1 to 3 ft) tall. The pollen grains are 20 to 21 μm in diameter and resemble those of giant ragweed. *Ambrosia psilostachya*, western ragweed, grows to a height of 30 to

120 µm (1 to 4 ft). It has the largest pollen grains of all the ragweeds, ranging from 22 to 25 µm in diameter. *Franseria acanthicarpa*, false ragweed, is found mainly in the South and Southwest, where it may cause allergic symptoms. *Franseria tenuifolia*, slender ragweed, is another allergenic species of this tribe. Ragweed sensitization can also result in cross-reactivity to a variety of fruits and vegetables (particularly cucumber, cantaloupe, watermelon, and banana), contributing to symptoms of PFS (57).

■ **FIGURE 6.11** Short ragweed (*Ambrosia artemisiifolia*). Close-up of staminate head. The anthers are full of pollen just before anthesis. (Courtesy of Arnold A. Gutman, MD, Associated Allergists Ltd., Chicago, IL.)

■ FIGURE 6.12 Scanning electron photomicrograph of ragweed pollen. Notice the pore on the pollen grain (*lower right*). (Courtesy of D. Lim, MD, and J.I. Tennenbaum, MD.)
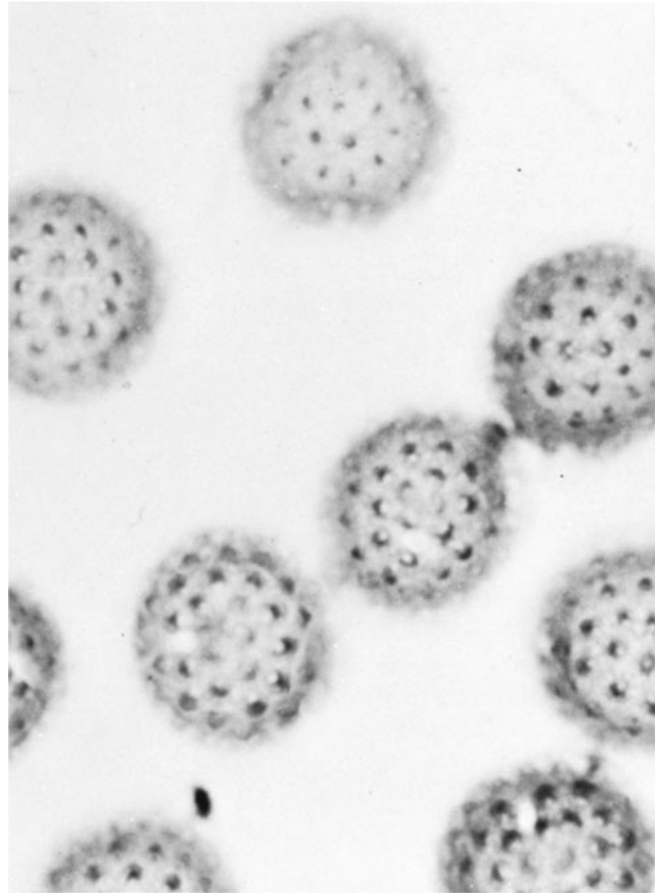
■ FIGURE 6.13 Short ragweed (*Ambrosia artemisiifolia*). Average diameter is 20 μm. Pollen grains have spicules on the surface. (Courtesy of Schering Corporation, Kenilworth, NJ.)

Xanthium (cocklebur) is morphologically distinct from the ragweeds, but its pollen grains are similar ranging in size from 20 to 30 μm with spine vestiges. Most species of *Xanthium* produce scanty pollen and are relatively unimportant causes of allergic rhinitis. Many patients with ragweed sensitivity also give strong skin test reactions to the cockleburs; this is probably a cross-reaction. It is found over much of North America and flowers during late summer season when daylight duration has declined.

Cyclachaerna xanthifolia, burweed marsh elder, is antigenically distinct from ragweed, and the pollen grains are morphologically different from those of ragweed (Fig. 6.14). All species are anemophilous, shed large quantities of pollen, and may cross react with ragweed. Pollen grains are oblate-spheroidal to prolate-spheroidal, 18 to 30 μm in size, have three to four pores, and a thick sexine.
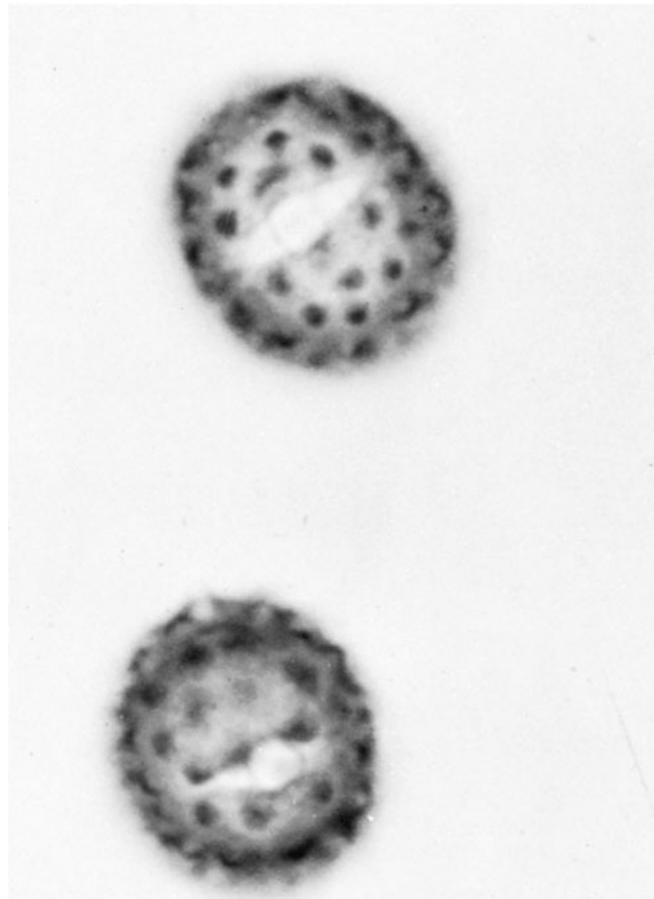
■ **FIGURE 6.14** Burweed marsh elder (*Cyclachaerna xanthifolia*). Average diameter is 19.3 μm. Three pores are centered in furrows, distinguishing it from ragweed. (Courtesy of Schering Corporation, Kenilworth, NJ.)

Tribe Anthemideae, or the mayweed tribe, is important to allergy because it contains chrysanthemums. Pyrethrum is an insecticide made from flowers of these plants, and inhalation of this substance may cause allergic symptoms in ragweed-sensitive persons as well as in those who have been sensitized to the pyrethrum itself. The genus *Artemisia* includes the sagebrushes, mugworts, and wormwoods and is one of the most important groups of allergenic weeds. *Artemisia vulgaris* is the common mugwort, found mainly on the east coast and in the Midwest in the United States. It is indigenous to Europe and Asia. The pollen grains, like those of other *Artemisia* species, are oblate spheroidal, 17 to 28 μm in diameter with three furrows and central pores, a thick exine, and essentially no spines. Other similar species are found on the West Coast and in the Southeast, Great Plains, and Rocky Mountains. *Artemisia tridentata* is common sagebrush, the most important allergenic plant of this tribe. It is most prevalent in the Great Plains and the Northwest, where overgrazing of grassland has increased its presence.

Polygonaceae (Buckwheat Family)

The docks, comprising the genus *Rumex*, are the only allergenic and anemophilous members of the buckwheat family. *Rumex acetosella* (sheep sorrel), *Rumex crispus* (curly dock), and *Rumex obtusifolius* (bitter dock) are the most important species. Pollen grains are oblate-spheroidal to prolate, range 20 to 30 μm in size, have three to four pores, and possess characteristic starch inclusion bodies. In the whole spectrum of pollen allergy, however, the docks are of minor significance.

Amaranthaceae (Pigweed and Waterhemp Family)

The best known of the amaranths are *Amaranthus retroflexus* (red-root pigweed), *Amaranthus palmeri* (careless-weed), and *Amaranthus spinosus* (spring amaranth). They are prolific pollen producers and should be considered in the etiology of "hay fever" in the areas where they abound. Western waterhemp (*Amaranthus tamariscinus*), a potent allergen, is most prevalent in the Midwest.

Chenopodiaceae (Goosefoot Family)

The genus *Chenopodium*, "goosefoot," is best represented by *Chenopodium album* (lamb's quarters) (Fig. 6.9). Each plant produces a relatively small amount of pollen, but in some areas the abundance of plants assures a profusion of pollen in the air. Indigenous to Europe, the chenopods were subsequently naturalized throughout North America. *Salsola pestifer*, Russian thistle, and *Kochia scoparia*, burning bush, are other Chenopodiaceae whose allergenic presence is more significant than that of lamb's quarters. Russian thistle is also known as tumbleweed because in the fall the top of the plant separates from its roots and is rolled along the ground by the wind. Burning bush may be recognized easily by the thin wing-like projections along its stems and, in the fall, by the fire engine red color of its leaves. It is often cultivated as an ornamental plant. Indigenous to Europe and Asia, these two weeds first became established in the prairie states but have migrated eastward, and are now important in the pathogenesis of pollinosis. *Atriplex* is the genus of the salt bushes, wingscale, and shadscale. These are of some allergenic significance in the Far West and Southwest.

Two crops numbered among the Chenopodiaceae are the sugar beet (*Beta vulgaris*) and spinach (*Spinacea oleracea*). The former has been implicated in allergy where it is cultivated.

Pollens of the Amaranthaceae and Chenopodiaceae are so morphologically similar that they are generally described as chenopod-amaranth when found in pollen surveys. Although subtle differences exist, it is generally fruitless and

impractical to attempt to identify them more precisely. They have the appearance of golf balls, which makes them unique and easy to identify (Fig. 6.15). Multiple pores give this peculiar surface appearance. The grains are 20 to 35 µm in diameter and spheroidal.
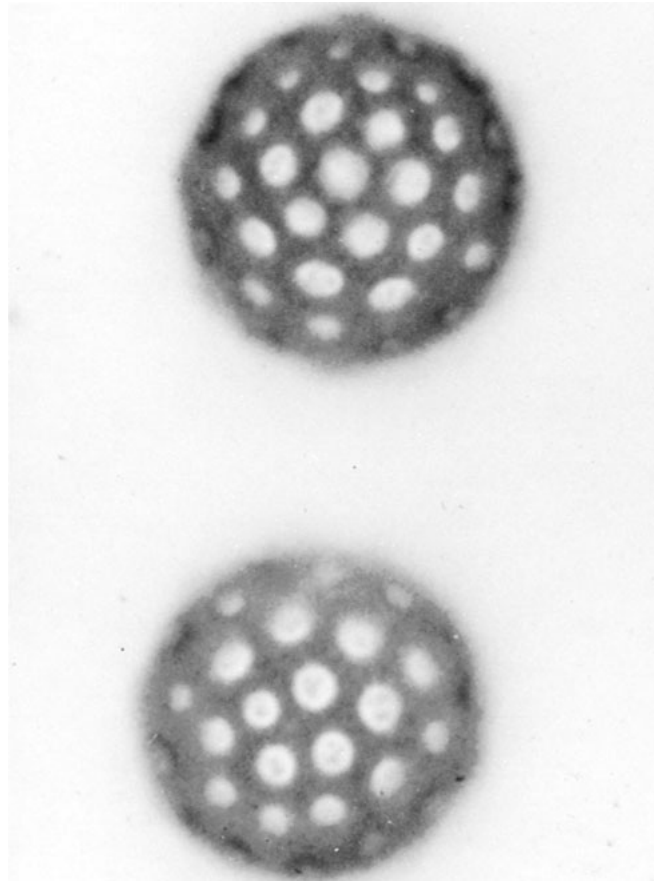
■ **FIGURE 6.15** Pigweed (*Amaranthus retroflexus*). Average diameter is 25 µm. The "golf ball" appearance of these grains is characteristic of the chenopod-amaranth group. (Courtesy of Schering Corporation, Kenilworth, NJ.)

Plantaginaceae (Plantain Family)

English plantain (*Plantago lanceolata*) is the only member of this family that is important for allergy. It sheds pollen mainly in May and June, corresponding to the time when grasses pollinate. The pollen grains may be distinguished by their multiple pores (numbering 7 to 14), a characteristic operculum, and variable size (25 to 40 µm) (Fig. 6.9). English plantain may be a potent cause of allergic rhinitis, which may be confused with grass pollinosis.

Urticaceae (Nettle Family)

Spreading pellitory (*Parietaria judaica*) and pellitory of the wall (*Parietaria officinalis*) have both been implicated in allergic disease. It is the leading cause of pollen sensitization in southern Europe, and is often referred to as the asthma

weed in Australia. It is native to the Mediterranean, but also found in coastal areas of the United Kingdom, Australia, and North America. The stinging nettle (Urtica) is the most common genus found in North America found in moist areas along streams and ditches. *Parietaria* species have a very long pollen season with peaks in the spring and fall. *Parietaria judaica* has a small (12 to 16 μm), triporate pollen.

Weed Pollen Allergens

King and Norman (58,59) were pioneers in the purification and analysis of allergens. *Amb a 1* (antigen E) and *Amb a 2* (antigen K), were purified by gel filtration and ion exchange chromatography, though currently *Amb a 1* and *Amb a 11* are considered ragweed major allergens while *Amb a 2* has been renamed *Amb a 1.05* and is considered an *Amb a 1* isoallergen. *Amb a 1* is mainly found in the intine of the pollen grain (60). Roughly 6% of the protein in ragweed extract is *Amb a 1*. There is no correlation between C content in six commercial preparations and quantitative studies of ragweed (61). However, *Amb a 1* can be quantified in allergenic extracts to determine potency using RAST inhibition. The U.S. Food and Drug Administration requires *Amb a 1* content to be labeled for ragweed allergen extracts. *Amb a 1* consists of two fragments that are easily dissociated, though they are resistant to enzymatic degradation. The amount of *Amb a 1* produced by an individual ragweed plant appears to be determined genetically. There is considerable variation in the amount extractable by standard methods from pollen from plants grown under identical conditions (59 to 468 μg/mL) (62). About 95% of ragweed allergic patients showed IgE binding to *Amb a 1* in rast inhibition assays (63).

Since the isolation of *Amb a 1* and its isoallergen, additional minor allergens have been identified. In contrast to *Amb a 1*, these low-molecular-weight fractions are rapidly extractable (<10 minutes) from pollen and have basic isoelectric points (64). *Amb a 3*, a plastocyanin (copper-containing protein involved in electron transfer), has a relatively high carbohydrate content, making it similar to certain grass pollen antigens. It consists of a single peptide chain of 102 amino acids. Two variants of *Amb a 3* differing by a single amino-acid residue have been described; however, this difference does not alter the allergenic specificity (65). Individuals who are allergic to *Amb a 3* have elevated IgE levels and are more likely to have the HLA-A2 and HLA-B12 phenotype (66).

Amb a 5 consists of a single polypeptide chain whose 45 amino acids have

been sequenced. The two isoallergenic forms differ at the second position by the substitution of leucine for valine in about 25% of samples. The frequency of positive skin test results to these antigens in ragweed-sensitive subjects demonstrates that approximately 90% to 95% react to *Amb a 1,* 20% to 25% react to *Amb a 3* and *Amb a 6,* and about 10% to *Amb a 5.* A small fraction (10%) of ragweed-sensitive patients is more sensitive to *Amb a 3* and *5* than to *Amb a 1. Amb a 6* and *Amb a 7* show sequence homology to other plant proteins involved in lipid metabolism and electron transport, respectively. Recently, a cysteine protease, *Amb a 11,* was discovered in ragweed and found to have structural homology to other group 1 allergens found in house dust mite. *Amb a 11* was thought to be included in the *Amb a 1* fraction and is found in two-thirds of ragweed allergic individuals and constitutes a major allergen (67).

The remaining weed allergens are summarized in Table 6.1. Major allergens of giant ragweed (*A trifida*), *Amb t 5,* and Western ragweed (Amb p 5) have been identified (68). Other allergens that cause allergic rhinitis have been purified from additional weeds. These include *Sal p 1* from *S pestifer* (Russian thistle) (69), *Par j 1* and *Par j 2* from *Parietaria judaica* pollen (Coccharia) (70,71), and *Par o 1* from *Parietaria officinalis* (72). The cDNA for *Par j 1* and *Par o 1* also have been described (73,74). *Art v 1* and *Art v 2* from *A. vulgaris* (mugwort) also have been purified (75). Ragweed's minor allergen, *Amb a 4,* has a defensin-like protein domain with a proline-rich region that has structural homology and demonstrates cross-reactivity to mugwort's *Art v 1* (76,77).

Grass Pollen Allergens

Grass pollen sensitivity is a significant problem worldwide. Important temperate grass species involved in allergic reactions are *Lolium perenne* (ryegrass), *Phleum pratense* (timothy), *Poa pratensis* (june grass, Kentucky bluegrass), *Festuca pratensis* (meadow fescue), *Dactylis glomerata* (cocksfoot, orchard grass), *Agrostis tenuis* (redtop), and *Anthoxanthum odoratum* (sweet vernal). Subtropical grasses that are involved in allergy include *Sorghum halepense* (Johnson grass), and *Cynodon dactylon* (Bermuda grass). Grass allergens are generally remarkable for the high degree of cross-reactivity between species. Due to this cross-reactivity, the allergens were once referred to in groups 1 to 9 that were present in most species studied. Now, however, the grasses are named according to standard allergen nomenclature (1). Common grass pollen allergens are listed in Table 6.2.

Lol p 1 (ryegrass) and *Phl p 1* (timothy) are located in the outer wall and

cytoplasm of the pollen grains, but can also be found in starch granules (78). As discussed earlier, these granules release on contact with water and are small (3 μm diameter) enough to reach the lower airways. These allergens are referred to as the β expansions and have been characterized as cell-wall loosening agents (79). There is some debate whether these allergens have proteolytic activity. The group 1 allergens have significant cross-reactivity based on IgE RAST inhibition, crossed immunoelectrophoresis (CIE), monoclonal antibody mapping, and amino-acid sequence homology (80–83). In grass-pollen allergic individuals, specific IgE to Phl p 1 has a prevalence of >90% and was proposed to be an initiator molecule for grass pollen allergy such that it promotes the sequential development of antibody responses to other non-cross-reacting molecules from the same source, fostering the phenomenon of "molecular spreading" (84). Other studied group 1 members include *Poa p 1* (Kentucky bluegrass), *Cyn d 1* (Bermuda), *Dac g 1* (orchard), and *Sor h 1* (Johnson). These allergens are present in 90% to 95% of grass pollen–allergic patients by skin testing. Groups 2 and 3 cause reactions in 60% and 70% of patients (85).

Group 2 allergens include *Lol p 2*, a ryegrass allergen, which has been cloned and is present in about 45% of rye-grass allergic patients (86). *Lol p 3* and *Dac g 3* have both been cloned and have 84% identity, but the predicted secondary structures suggest they may not be cross-reactive (87). Only 20% of grass-pollen sensitive patients react to the group 4 allergen, which appears to have a significant cross-reactivity with *Amb a 1* (87). *Phl p 5* is present in excess of 95% of patients, but its functions are still not certain (1). The cDNA of *Cyn d 7* also has been cloned and has two calcium-binding sites. Depletion of calcium causes a loss of IgE reactivity (88). Profilin, a compound involved in actin polymerization, has been identified as an allergen in tree pollens (89). It is allergenic and also has been found to be a minor allergen in the grass allergens and is currently classified in *Phl p 12* and *Cyn d 12* (1). Thus far, subtropical grass pollen appear to lack the clinically relevant group 2 and group 5 allergens that are seen in temperate grass pollen (90).

The cDNA cloning of multiple grass allergens has some potential diagnostic applications. A strategy to take advantage of the extensive cross-reactivity between species using recombinant allergens has been studied. A mixture of *Phl p 1, Phl p 2, Phl p 5*, and *Bet v 2* (birch profilin) accounted for 59% of grass-specific IgE (91). A study of purified *Lol p 1* and *Lol p 5* versus recombinant *Phl p 1* and *Phl p 5* was performed on RAST-positive patients. The *Lol p* extracts reacted with 80% of the IgE, whereas the recombinant *Phl p* reacted with 57% of the IgE (92).

One of the most innovative applications of DNA technology has been the development of ryegrass plants with down regulation of the *Lol p 5* gene. This transgenic ryegrass pollen maintained its fertility, but had a significant decrease in its IgE-binding capacity compared with normal pollen. This creates the possibility of genetic engineering of less allergenic grasses (93).

Tree Pollen Allergens

There seems to be a higher degree of specificity to skin testing with individual tree pollen extracts compared with grass pollens because pollens of individual tree species may contain unique allergens. Despite this observation, several amino-acid homologies and antigenic cross-reactivities have been noted. Most tree pollen characterization has been done using birch (*Betula verrucosa*), alder (*Alnus glutinosa*), hazel (*Corylus avellana*), white oak (*Quercus alba*), olive (*Olea europaea*), and Sugi (*Cryptomeria japonica*) allergens. About 53 tree pollen allergens have been recognized and identified by the IUIS currently and common tree allergens are listed in Table 6.1. Tree pollen panallergens are those that are ubiquitously expressed and generally belong to the profilin (e.g., *Bet v 2*), polcalcin (e.g., *Bet v 4*), and pathogenesis-related protein class 10 (PR-10) (*Bet v* 1–related protein) families (Fig. 6.16). The clinical significance of these molecules has been argued extensively and no general consensus has been arrived. The sensitization rates to these molecules are relatively low and affected by level of exposure, geography, and the subject's age (51). These are discussed further here.

TABLE 6.2 GRASS POLLEN ALLERGENS

	FLOWERING PERIOD	GRASS GROUP 1(β-EXPANSIN)	GRASS GROUP 2(EXPANSIN-LIKE PROTEIN)	GRASS GROUP 3(EXPANSIN-LIKE PROTEIN)	GRASS GROUP 4(BERBERINE-BRIDGE ENZYME)	GRASS GRO (RIBONUCLE
Timothy grass *Phleum pratense*	5–8	*Phl p 1*[a]	*Phl p 2*[a]	*Phl p 3*[b]	*Phl p 4*[a]	*Phl p 5*[a]
Perennial ryegrass *Lolium*	5–8	*Lol p 1*	Lol p 2	*Lol p 3*	Lol p 4	*Lol p 5*

perenne						
Orchard grass *Dactylis glomerata*	5–6	*Dac g 1*	Dac g 2	*Dac g 3*	*Dac g 4*	*Dac g 5*
Kentucky blue grass *Poa pratensis*	5–8	*Poa p 1*				*Poa p 5*
Bermuda grass *Cynodon dactylon*	All season	*Cyn d 1*[a]				
Bahia grass *Paspalum notatum*	All season	*Pas n 1*				
Johnson grass *Sorghum halepense*	All season	*Sor h 1*	Sor h 2			

Major allergens highlighted in italics.

[a]Available for single- and multiplex analysis.

[b]Allergen not officially acknowledged by the WHO/IUIS allergen nomenclature sub-committee.

From Pablos I, Wildner S, Asam C, et al. Pollen allergens for molecular diagnosis. *Curr Allergy Asthma Rep*. 2016;16:31.

A major birch-pollen allergen, *Bet v 1*, has been isolated by a combination chromatographic technique. Both the amino-acid sequence as well as a cDNA clone coding for the *Bet v 1* antigen have been described (94). *Bet v 1* (birch), *Aln g 1* (alder), *Car b 1* (hornbeam), *Ost c 1* (hop-hornbeam), *Cor a 1* (hazelnut),

Fag s 1 (beech), *Cas s 1* (chestnut), and *Que a 1* (oak), all belong to PR-10 family of molecules encoded by a diverse multigene family (51). A tree-pollen allergen cluster schematic is shown in Figure 6.16 (51). *Bet v 1* is the birch tree allergen that cross-reacts with a low-molecular-weight apple allergen, a discovery that helps to explain the association between birch sensitivity and oral apple sensitivity (95). Further investigations by the same workers extend this cross-reactivity to include pear, celery, carrot, and potato allergens. Most of the 20 patients tested had birch-specific serum IgE (anti–*Bet v 1* and anti–*Bet v 2*) that cross-reacted to these fruits and vegetables. *Bet v 2* has been cloned and identified as profilin, a compound responsible for actin polymerization in eukaryotes. There is approximately 33% amino-acid homology between the human and birch profilin molecules (89).

Bet v 3 and *Bet v 4* have both been cloned and further described as calcium-binding molecules called polcalcins (96,97). *Bet v 7* is the most recent to be cloned. It reacts with IgE from 20% of birch allergic patients and has been identified as a cyclophilin (98).

Cryptomeria japonica, the national tree of Japan, is a significant source of allergenic pollen. For a long time, this tree was incorrectly called Japanese cedar, though it is a member of the cypress family. It is distinct from Japanese cypress and is now simply called by its Japanese name, Sugi. Its major allergen, *Cry j 1* —a pectate lyase, was initially separated by a combination of chromatographic techniques. Four subfractions were found to be antigenically and allergenically identical (99). There is some amino-acid homology between *Cry j 1* and *Amb a 1,* but the significance of this is unclear. A second Sugi allergen, *Cry j 2*—a polygalacturonase, also has been described (100). Allergens from mountain cedar (*Juniperus ashei*) are important in the United States. The major allergen, *Jun a 1,* has a 96% homology with *Cry j 1* and some homology with Japanese cypress (*Chamaecyparis obtusa*) (101). Olive tree pollen is an important allergen in the Mediterranean and California. *Ole e 1* through *Ole e 11* have all been described (102). Mesquite trees (*Prosopis juliflora*), of the order Fabales, are a source respiratory allergies in India, North America, and the Arabian Peninsula. Mesquite pollen allergens appear to show a high rate of cross-reactivity to acacia (wattle) tree allergens based on inhibition studies with pollen extracts (103).
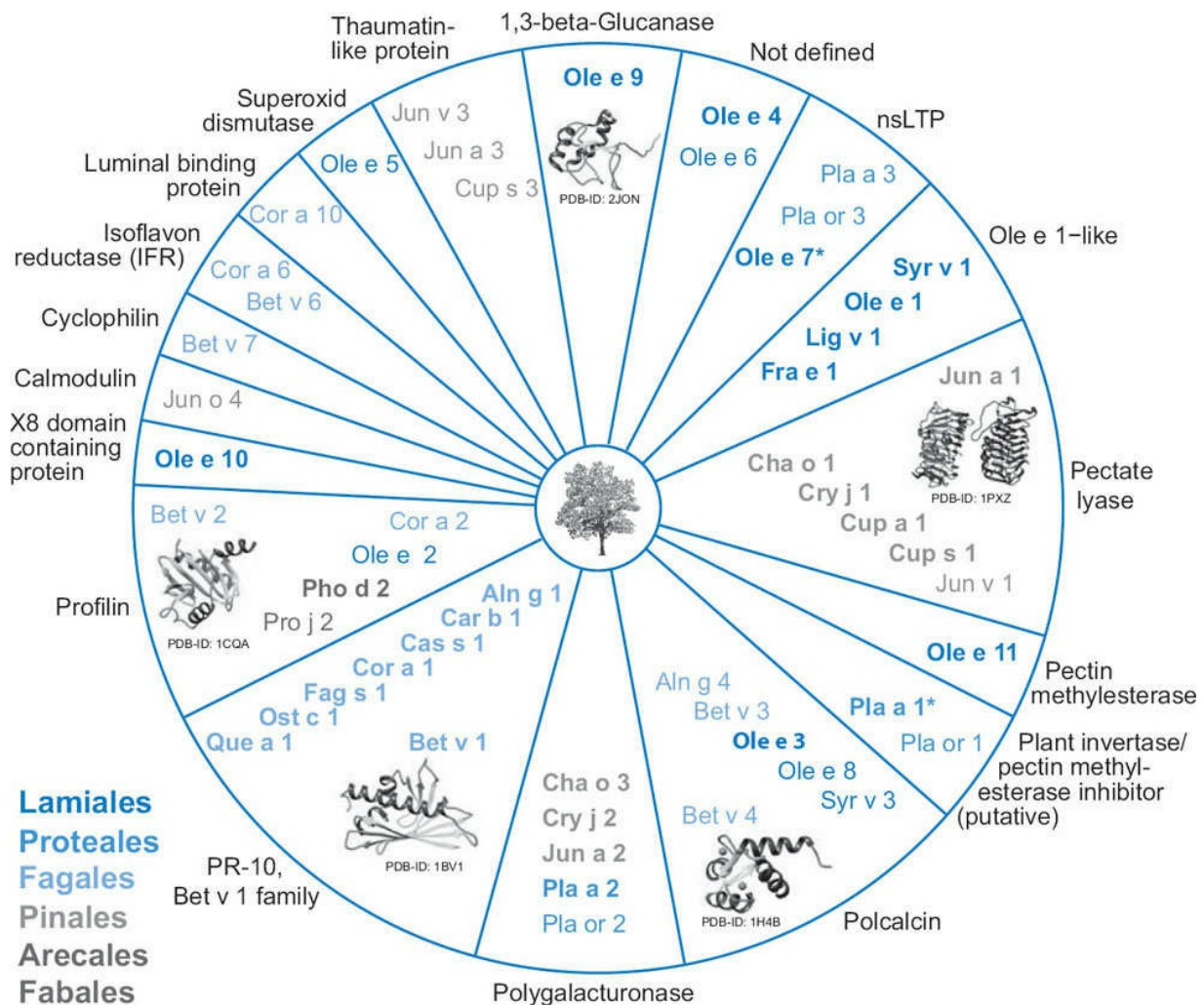
FIGURE 6.16 Tree pollen allergens cluster. (Figure 2 from Asam C, Hofer H, Wolf M, et al. Tree pollen allergens—an update from a molecular perspective. *Allergy*. 2015;70[10]:1201–1215.)

ROLE OF FUNGAL ALLERGENS

Sensitivity to fungal allergens has been recognized since the 1700s when Sir John Floyer noticed asthma in individuals exposed to musty environments in wine cellars. Over the years, the role of fungal sensitization and exposure in allergic respiratory disease has been identified as an important factor, particularly in the development, persistence, and severity of asthma. Several reports over the past few decades have established a relationship between fungal sensitization and exposure with the development of asthma in adults (104) and children (105). Sensitization to *Alternaria* at age 6 years is associated with persistent asthma into adulthood (106); sensitization to fungi has also been associated with asthma severity and potentially fatal asthma (107–109). Lastly, epidemics of asthma exacerbation have been linked to increased airborne fungal spores during thunderstorms (48).

The overall prevalence of fungal sensitivity is still unclear. In a study of 102 atopic U.S. citizens, 21% were sensitized to one or more fungal allergens based on positive skin tests (110). Various studies report 12% up to 80% of atopic patients are sensitized to fungi (111,112). A major limitation of epidemiological studies is the lack of standardized reagents for skin testing. Newer diagnostic tests, such as microarrays using purified fungal allergens, may allow for better assessment of allergic sensitizations to fungi.

Exposure to fungal allergens and other fungal products occurs both in outdoor and indoor environments. Sensitization and innate immune responses to these fungal elements resulting in allergic respiratory diseases can occur in both environments (113). Estimates of fungal exposure are largely based on volumetric spore counts using microscopy to identify fungal species, however, it may be difficult to differentiate certain fungi (e.g., *Aspergillus* vs. *Penicillium* species) based on spore morphology. Other methods such as fungal cultures or DNA analysis may be necessary. Nevertheless, exposure to fungal spores outdoors typically exceeds indoor spore counts by 100- to 1,000-fold. In some instances, i.e., gross fungal contamination of the indoor environment can lead to high indoor spore counts. In temperate climates, fungal spores can be found in atmospheric surveys during snow-free periods with peaks often in late summer and fall. This prolonged period of exposure presents problems for the clinician attempting to diagnose fungal allergic disease because the exposure tends to be fairly continuous in contrast to pollen sensitivity which has more defined seasons. Specific exposure to fungi, such as raking leaves, may give some clues to the diagnosis. Worsening of symptoms may occur during damp weather due to the release of ascospores. Interestingly, absolute spore counts often decrease during a rainstorm because spores are "washed out" similar to pollen grains. As mentioned previously, epidemics of asthma exacerbation may occur during thunderstorms because of updrafts carrying fungal spores (48). Several important fungal allergenic species (*Alternaria, Cladosporium*) release spores during dry windy periods. Snow cover generally obliterates outdoor fungal spores, but thaws can contribute to fungal growth and sporulation.

Exposure to indoor fungi generally reflects outdoor exposure when windows are open. Point source indoor fungal exposure is often the consequence of water leaks or excessive moisture. Several studies indicate that early life exposure to indoor fungi is associated with the development of asthma in young children and increased morbidity in those with current asthma (113). It should be remembered that damp environments are also associated with house dust mite proliferation and microbial growth.

FUNGAL TAXONOMY

Molecular biology approaches, especially DNA-sequencing and multiple microarrays for specific IgE antibodies to purified fungal allergens, have revolutionized fungal taxonomy. In the past, fungi were classified by their sexual state morphology, which lead to the now obsolete category of deuteromycetes (fungi imperfecti) that lack an obvious sexual stage. Other organisms previously categorized as fungal-like (myxomycetes = slime molds and oomycetes = water molds) have been moved to other kingdoms.

Currently, eight phyla of fungi are recognized, of which three produce important aeroallergens (114). These three phyla are Zygomycota, Ascomycota, and Basidiomycota. The close phylogenetic relationships among genera within these phyla are reflected in extensive IgE cross-reactivity within each taxon (Fig. 6.17).

The following section discusses some characteristics of some of the important fungal allergen sources.

Phylum Zygomycetes

This phylum contains about 1,060 species. The sexual forms of Zygomycetes are characterized by thick-walled spinous zygospores; the asexual forms are characterized by sporangia. Spores of this group generally are not prominent in the air but can be found in abundance in water-damaged buildings, around composting vegetables, and in cheese making. The order Mucorales includes the allergenic species *Rhizopus nigricans* and *Mucor racemosus*. *Rhizopus nigricans* is the black bread mold whose hyphae are colorless but whose sporangia (visible to the naked eye) are black.

Phylum Ascomycetes

This phylum contains over 65,000 species. The Ascomycetes are the "sac fungi." Their spores are produced in spore sacs called asci. Concentrations of ascospores reaching thousands of particles per cubic meter occur in many areas and are especially numerous during periods of high humidity (e.g., after rain). Conidia produced by these fungi are wind dispersed which include many species previously classified as Deuteromycetes, which are sources of important fungal allergens. The class Saccharomycetes contains the species *Candida albicans*, a yeast, occasionally associated with allergic diseases, but more commonly with infections.

FIGURE 6.17 Fungal taxonomy. (Figure 1 from Knutsen A, Bush RK, Demain J, et al. Fungi and allergic lower respiratory tract diseases. *J Allergy Clin Immunol*. 2012;129:280–291.)

■ FIGURE 6.18 *Cladosporium* species. Average spore size is 4 × 16 μm. Spores occur in chains and have small attaching collars at one end. The first spore buds off from the conidiophore, then the spore itself buds to form a secondary spore. (Courtesy of Bayer Allergy Products [formerly Hollister-Stier Labs], Spokane, WA.)

Geotrichum species and *Candida albicans* are a part of the human microbiome which may cause infections and occasionally allergic diseases. *Saccharomyces cerevisiae,* also known as baker's or brewer's yeast, can induce IgE-mediated diseases (allergic rhinitis, asthma), hypersensitivity pneumonitis, and occupational asthma.

The class Dothideomycetes contains the genus *Cladosporium* of which there are over 750 species. *Fulvia* and *Hormodendicum* are archaic terms for this genus. *Cladosporium* (Fig. 6.18) spores are among the most abundant fungi in outdoor air surveys throughout the year with low concentrations in winter. *Cladosporium herbarum* is in outdoor air surveys. *Cladosporium spherospermum* and *C. halotolerans* can be found as indoor growth sources on wet building materials (114).

Within the class Dothideomycetes is the family Pleosporaceae, a source of many commonly recognized allergenic fungi. The genus *Alternaria* with over 270 species is well recognized as an important factor in allergic respiratory disease, especially asthma (107). *Alternaria alternata* has received the most research attention. The spores of *Alternaria* are distinctive morphologically (Fig.

6.19) and are widely distributed in outdoor air with peak spore counts being found in late summer to fall, particularly on dry, windy days. *Alternaria* may also be found indoors on damp building materials.
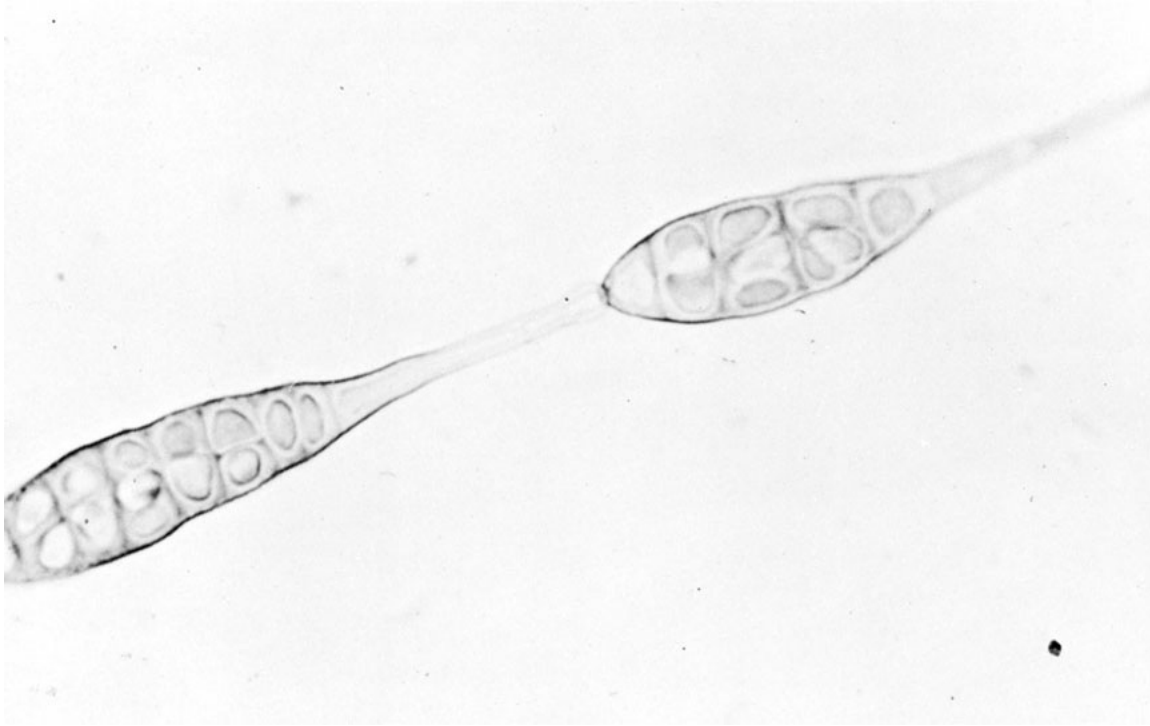
■ **FIGURE 6.19** *Alternaria alternata*. Average spore size is 12 × 33 µm. Spores are snowshoe-shaped and contain transverse and longitudinal septae with pores. (Courtesy of Schering Corporation, Kenilworth, NJ.)

■ FIGURE 6.20 *Helminthosporium* species. Average spore size is 15 × 75 mm. The spores, which occur in the ends of the conidiophores, are large, brownish, and have transverse septae. (Courtesy of Schering Corporation, Kenilworth, NJ.)

A closely related group with the Pleosporaceae, known as the bipolaris complex, consists of the genera *Drechslera, Bipolaris, and Helminthosporium*, which can be separated on the basis of spore morphology and other features (Fig. 6.20). All have been associated with allergic respiratory diseases with bipolaris frequently linked to allergic fungal sinusitis (AFS).

Exserohilum rostrata is the present name for the species previously identified as *Helminthosporium rostratum, Bipolaris rostratum,* or *Drechslera rostrata*. The significance of this plant pathogen in allergic disease has yet to be ascertained.

Other Pleosporaceae, *Curvularia* and *Stemphylium* (Fig. 6.21), species can be found principally in outdoor air samples but usually not in abundant amounts. Both genera appear to have IgE cross-reactivity with *Alternaria* allergens. The class of Dothideomycetes includes the genera *Phoma* and *Epicoccum* which have yet to be assigned a specific family name. *Phoma* species include 270 taxa; some IgE cross-reactivity exists between *Phoma* and *Alternaria. Epicoccum nigrum* (previously *E. purpurascens*) (Fig. 6.22) is often encountered in outdoor air surveys and follows distribution patterns similar to *Alternaria*. Sensitivity is associated with allergic respiratory disease and AFS.

The family Dothioraceae contains the genus *Aureobasidium* (formerly *Fullularia*). *Aureobasidium pullulans* occurs in outdoor and indoor house dust samples. Sensitivity has been linked to allergic respiratory disease (114).
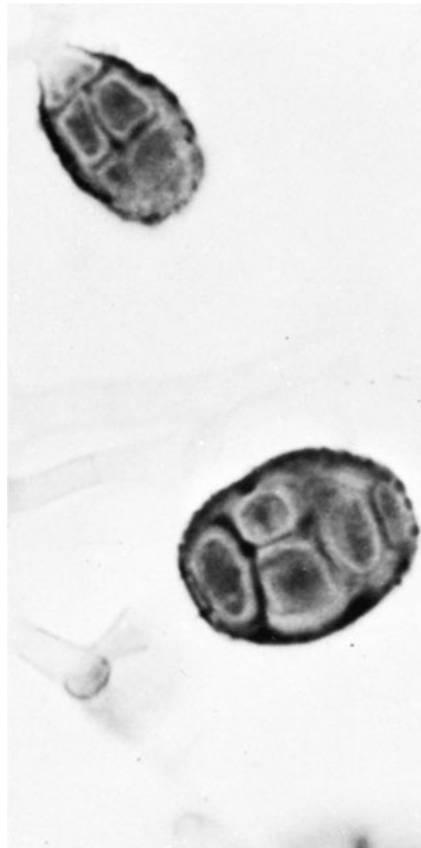
■ **FIGURE 6.21** *Stemphylium* species. The spores superficially resemble those of *Alternaria* but lack the "tail" appendage. Also, they are borne singly rather than in chains. (Courtesy of Schering Corporation, Kenilworth, NJ.)

The class Eurotiomycetes includes the genera *Aspergillus* and *Penicillium*, which are important allergens in allergic respiratory disease including allergic bronchopulmonary aspergillosis (ABPA). Both *Aspergillus* (Fig. 6.23) and *Penicillium* (Fig. 6.24) are common airborne fungi and can be encountered in indoor environments as well. Because the spores of both genera are similar in morphologic appearance, culture techniques or DNA analysis may be necessary to properly identify which organism is which. *Aspergillus fumigatus* and *Penicillium chrysogenum* are actually four species of which only one is commonly found in damp indoor environments. The *P. chrysogenum* is the proper name currently used instead of the archaic usage *P. notatum. Penicillium* and *Aspergillus* allergens are highly cross-reactive (see discussion of fungal allergens further).
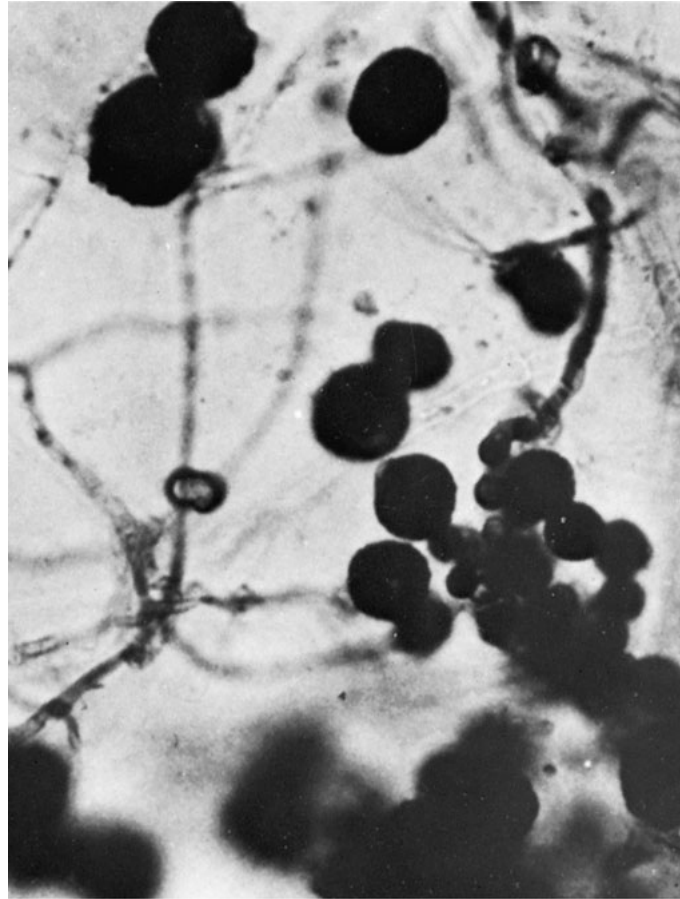
■ **FIGURE 6.22** *Epicoccum nigrum*. Average diameter is 20 μm. Large spores are borne singly on the ends of conidiophores. They are yellowish brown and rough, and develop transverse septae when old. (Courtesy of Bayer Allergy Products [formerly Hollister-Stier Labs], Spokane, WA.)
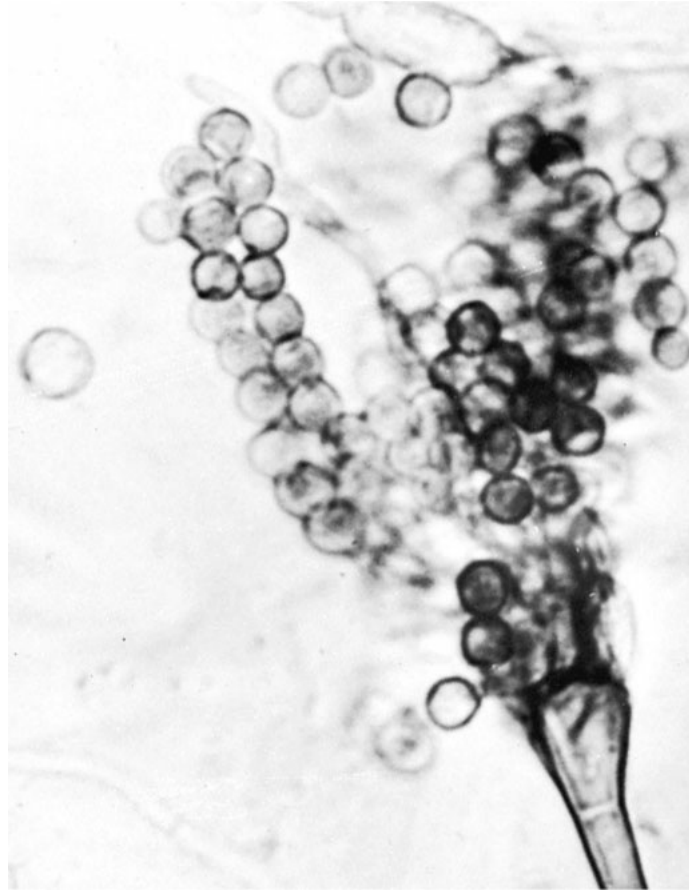
■ **FIGURE 6.23** *Aspergillus* species. Average spore diameter is 4 μm. The spores are borne in chains and have connecting collars. (Courtesy of Bayer Allergy Products [formerly Hollister-Stier Labs], Spokane, WA.)
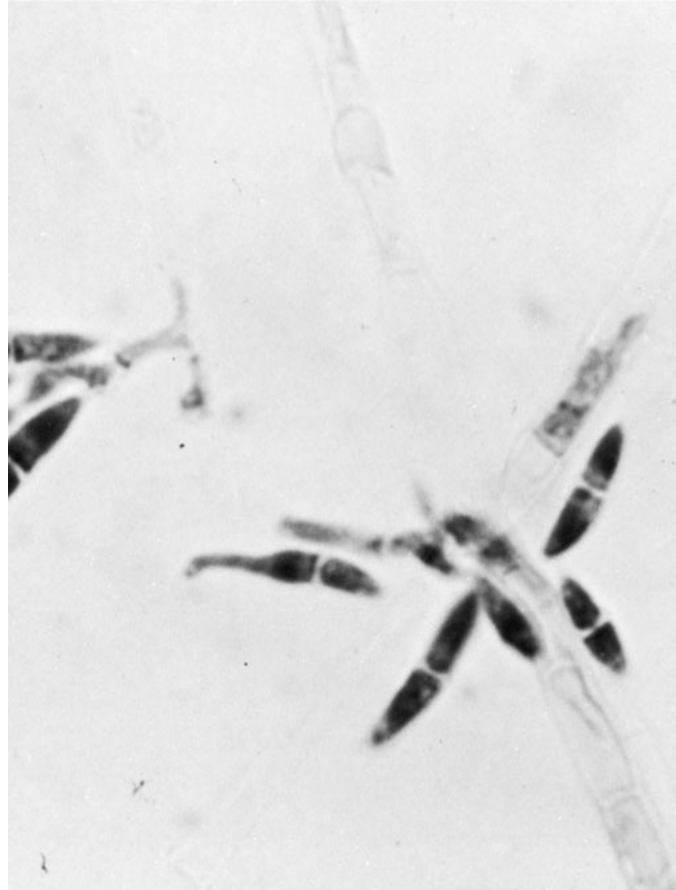
Other genera within the class Eurotiomycetes are *Trichophyton* and *Epidermophyton*, which are linked to cutaneous infections and less commonly with respiratory disease.

The class Sordariomycetes contains a number of genera that produce fungal allergens. The genus *Fusarium* produces spores that are airborne largely in wet weather (Fig. 6.25). Sensitivity is associated with allergic respiratory diseases. The genus *Trichoderma* grows in soil and has been found in damp building material. *Trichoderma* sensitivity is associated with rhinitis, asthma, and AFS. The genus *Stachybotrys* has caused concern because of its potential to produce

myotoxins (so-called toxic black mold). IgE sensitization can occur, but the "toxic" effects are highly controversial (114).

The genus *Chaetornium* is not infrequently isolated from water-damaged indoor materials. Its role in allergic diseases is not well established because no purified allergens have been identified to date.

The genera *Acremonium* and the more restrictive genera *Cephalosporium* play limited roles in allergic respiratory diseases.

The genera *Chrysonilia* (formerly *Monilia*) and *Neurospora* have been chiefly linked to occupational lung diseases, e.g., *C. sitophilia*, the pink bread mold, in bakers, and *Neurospora* species in coffee, saw mill, and cork workers.

The genus *Botrytis* is a common plant pathogen. Sensitivity to *B. cinerea* has been linked to asthma severity (114).

PHYTUM BASIDIOMYCOTA

The phylum Basidiomycota contains over 30,000 species. High levels of basidiospores in the outdoor air have been linked to epidemic episodes of asthma. While several allergens have been identified, commercially available materials for skin testing are limited. Many species are difficult to grow in culture, which contributes to this problem.

Although species of the genera *Rhodotorula* are recognized, *R. mucilaginosa* (formerly *R. rubra*) appears to be the most important clinically. Lastly, the genus *Ustilago* and other smut fungi (*Sporisorium* and *Sphacelotheca*) belong to the family Ustilaginaceae. Ustilago is a frequent plant pathogen of corn (corn smut), and positive intradermal skin tests to *U. maydis* extracts have been reported (114).

Fungal Allergens

Unfortunately, the ability of clinicians to diagnose fungal allergy has been limited owing to the lack of standardized fungal extracts for skin testing and the continued use of archaic terminology (e.g., *P. notatum*) for fungal taxa. Just as DNA sequencing has revolutionized fungal taxonomy and phylogeny, the use of molecular biology techniques to purify and clone fungal allergens has been highly significant (Table 6.3). The use of microarrays with purified fungal allergens to assay for specific IgE antibodies in sera of individuals with respiratory disease demonstrates a high degree of IgE cross-reactivity between fungal allergens and the close phylogenetic relationships among fungi (115).

In addition, purification of fungal allergens reveals the family of proteins to which they belong (Table 6.3). In addition to IgE-binding allergens, fungal allergens and other fungal products can activate innate immune responses leading to asthma (116).

Major allergens have been isolated from a number of fungi important in allergic diseases. *Alt a 1* from *Alternaria alternata* is of unknown biological activity; cross-reactive allergens to it have been obtained from *Stemphylium, Epicoccum,* and other genera. *Cla h 1* from *Cladosporium herbarum* is a major allergen, and when employed in skin testing reagents significantly increases positive responses. *Asp f 1* from *Aspergillus fumigatus* is a ribotoxin (mitogillin), important in ABPA and *Aspergillus*-related asthma. A large number of *Aspergillus* and *Penicillium* allergens have been purified which are often highly cross-reactive. Many of these have protease activity, such as vacuolar serine protease (*Asp f 18, Pen c 18*), metalloprotease (*Asp f 5*), alkaline serine protease (*Asp f 13, Pen c 13*), aspartyl protease (*Asp f 10*), enolase (*Alt a 6, Cla h 6, Asp f 22*), manganese superoxide dismutase (*Asp f 6*), glutathione-*S*-transferase (*Alt a 13, Pen c 24*), and various dehydrogenases (*Alt a 10, Cla h 8, Cla h 3*). Further advances in the isolation and characterization of fungal allergens will clarify their role in allergic diseases and improve diagnostics available to clinicians and epidemiologists.

DUST MITES

House dust has long been recognized to be a source of respiratory allergy. It dates back to 1921 when Kern described patients who had skin test reactivity to house dust extracts taken from their own residence (117). However, it was not until the 1960s, when several Dutch workers demonstrated that dust mites (specifically *Dermatophagoides pteronyssinus*) were the allergens in house dust and elaborated on those relationships (118). Mites are small (0.2 to 0.3 mm long), eight-legged animals that are not visible to the naked eye, but easily identified microscopically using a low-power lens. They are a subclass of arachnids that constitute several orders of Acarina, and belong to the family Pyroglyphidae. The primary dust mites found inside homes in North America and Europe are *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus.* Other house dust mite species are *Dermatophagoides microceras, Euroglyphus maynei,* and the tropical *Blomia tropicalis.* A male house mite can have a life span of about 10 to 20 days while females can live up to 70 days. They can lay between 30 and 100 eggs over their life span and produce about 2,000 fecal particles making them a prolific contributor to allergy. Dust mites

feed off shed human skin, organic detritus, and other high protein debris in their environment. They obtain water from the ambient water in the air.

TABLE 6.3 FUNGAL ALLERGENS

FUNGAL SPECIES	ALLERGEN	MOLECULAR WEIGHT (kDa)	BIOLOGICAL ACTIVITY
Phylum Ascomycota			
Alternaria alternata	Alt a 1	28	
	Alt a 3		Heat shock protein 70
	Alt a 4	57	Disulfide isomerase
	Alt a 5	11	Ribosomal protein P2
	Alt a 6	45	Enolase
	Alt a 7	22	YCP4 protein
	Alt a 8	29	Mannitol dehydrogenase
	Alt a 10	53	Aldehyde dehydrogenase
	Alt a 12	11	Acid ribosomal protein P1
	Alt a 3	26	Glutathione-*S*-transferase
Aspergillus flavus	Asp fl 13	34	Alkaline serine protease

Aspergillus fumigatus	Asp f 1	18	Mitogillin family
	Asp f 2	37	
	Asp f 3	19	Peroxysomal protein
	Asp f 4	30	
	Asp f 5	40	Metalloprotease
	Asp f 6	26.5	Mn superoxide dismutase
	Asp f 7	12	
	Asp f 8	11	Ribosomal protein P2
	Asp f 9	34	
	Asp f 10	34	Aspartate protease
	Asp f 11	24	Peptidyl-prolyl isomerase
	Asp f 12	90	Heat shock protein P90
	Asp f 13	34	Alkaline serine protease
	Asp f 15	16	
	Asp f 16	43	

	Asp f 17		
	Asp f 18	34	Vacuolar serine protease
	Asp f 22	46	Enolase
	Asp f 23	44	Ribosomal protein L3
	Asp f 27	18	Cyclophilin
	Asp f 28	13	Thioredoxin
	Asp f 29	13	Thioredoxin
	Asp f 34	20	PhiA cell wall protein
Aspergillus niger	Asp n 14	105	β-xylosidase
	Asp n 18	34	Vacuolar serine protease
	Asp n 25	66–100	3-phytase B
Aspergillus oryzae	Asp o 13	34	Alkaline serine protease
	Asp o 21	53	TAKA-amylase A
Aspergillus versicolor	Asp v 13	43	Extracellular alkaline serine protease
Candida albicans	Cand a 1	40	Alcohol dehydrogenase

	Cand a 3	20	Peroxysomal protein
Candida boidinii	Cand b 2	20	Peroxysomal membrane protein A
Cladosporium cladosporioides	Cla c 9	36	Vacuolar serine protease
	Cla c 14	36.5	Transaldolase
Cladosporium herbarum	Cla h 2	45	
	Cla h 5	11	Acid ribosomal protein P2
	Cla h 6	46	Enolase
	Cla h 7	22	YCP4 protein
	Cla h 8	28	Mannitol dehydrogenase
	Cla h 9		Vacuolar serine protease
	Cla h 10	53	Aldehyde dehydrogenase
	Cla h 12	11	Acid ribosomal protein P1
Curvularia lunata	Cur l 1	31	Serine protease
	Cur l 2	48	Enolase

	Cur l 3	12	Cytochrome c
	Cur l 4	54	Vacuolar serine protease
Epicoccum purpurascens	Epi p 1	30	Serine protease
Fusarium culmorum	Fus c 1	11	Ribosomal protein P2
	Fus c 2	13	Thioredoxin-like protein
Penicillium brevicompactum	Pen b 13	33	Alkaline serine protease
	Pen b 26	11	Acidic ribosomal protein P1
Penicillium chrysogenum	Pen ch 13	34	Alkaline serine protease
	Pen ch 18	32	Vacuolar serine protease
	Pen ch 20	68	*N*-acetylglucosaminidase
	Pen ch 31		Calreticulin
	Pen ch 33	16	
	Pen ch 35	36.5	Transaldolase
Penicillium citrinum	Pen c 3	18	Peroxysomal membrane protein

	Pen c 13	33	Alkaline serine protease
	Pen c 19	70	Heat shock protein P70
	Pen c 22	46	Enolase
	Pen c 24		Elongation factor 1 β
	Pen c 30	97	Catalase
	Pen c 32	40	Pectate lyase
Penicillium oxalicum	Pen o 18	34	Vacuolar serine protease
Stachybotrys chartarum	Sta c 3	21	Extracellular alkaline Mg-dependent exodesoxyribonuclease
Trichophyton rubrum	Tri r 2		Putative secreted alkaline protease Alp 1
	Tri r 4		Serine protease
Trichophyton tonsurans	Tri t 1	30	
	Tri t 2	83	Serine protease
Phylum Basidiomycota			
Coprinus comatus	Cop c 1	11	Leucine zipper protein

	Cop c 2		Thioredoxin
	Cop c 3		
	Cop c 5		
	Cop c 7		
Malassezia furfur	Mala f 2	21	Peroxysomal membrane protein
	Mala f 3	20	Peroxysomal membrane protein
	Mala f 4	35	Mitochondrial malate dehydrogenase
Malassezia sympodialis	Mala s 1		
	Mala s 5		
	Mala s 6		Cyclophilin
	Mala s 7		
	Mala s 8		
	Mala s 9		
	Mala s 10	86	Heat shock protein 70
	Mala s 11	23	Manganese superoxide dismutase

	Mala s 12	67	Glucose-methanolcholine oxidoreductase
	Mala s 3	13	Thioredoxin
Psilocybe cubensis	Psi c 1		
	Psi c 2	16	Cyclophilin
Rhodotorula mucilaginosa	Rho m 1		Enolase
	Rho m 2	47	Vacuolar serine protease

Current as of April 29, 2010 (http://www.allergen.org). From Knutsen A, Bush RK, Demain J, et al. Fungi and allergic lower respiratory tract diseases. *J Allergy Clin Immunol*. 2012;129:280–291.

In North America, dust mites appear to grow more rapidly in the summer months. The major factors governing mite reproduction are ambient temperature and humidity. When the relative humidity is greater than 60% at 21°C (70°F) dust mites tend to grow (119). If the relative humidity falls below 40% to 50% for more than 11 days, adult dust mites are unable to survive at temperatures above 25°C (77°F), because increased transpiration of water leads to dehydration (120). The larval form (protonymph) of *D. farinae*, however, is resistant to desiccation and may account for the resurgence of dust mites after the winter heating season.

Regional patterns have been observed in dust mite species distribution. High altitudes are associated with low number of dust mites, presumably because of the reduced humidity (121). Areas with a long dry season favor growth of *D. farinae*, but humid areas favor *D. pteronyssinus*. *E. maynei* will sometimes be the predominant species under damp conditions. *B. tropicalis* is important in the southeastern United States (e.g., Florida) as well as in Central and South America.

Dust mites typically are found in the greatest numbers in mattress dust, but

can certainly be found anywhere in the house that people routinely traffic, including rugs, bedding, and furniture. Housekeeping or the presence of household pets does not necessarily influence the mite load. The primary methods recommended to reduce dust mites include nylon or polyester-based impermeable mattress and pillow encasings, frequent washing of bedding, and maintenance of ambient humidity at less than 40% to 50%. Whether dust mite control measures have a significant clinical effect is no longer a point of controversy; the most recent 2013 practice parameters by the Joint Task Force (AAAAI and ACAAI) recommend the earlier control measures (122,123).

Both the mite body and the feces contain allergen, though the major allergens are found in feces extracts. A high percentage of dust mite–sensitive patients have positive skin tests to both *D. farinae* and *D. pteronyssinus*. Studies show that many allergens cross-react between the two species although some are unique (124).

Group 1 dust mite allergens include *Der p 1, Der f 1, Der m 1,* and *Eur m 1*. These allergens have 80% to 85% homology among the mite species, with moderate levels of antigenic cross-reactivity measured by IgE antibodies. Studies of *Der p 1,* a 24-kDa glycoprotein, suggest that it is responsible for 75% of the IgE binding in mite feces (125). Using sequence data, the group 1 allergens have been identified as members of the cysteine protease family, and the possible importance of this function is addressed earlier in the chapter. The group 2 allergens include *Der p 2* and *Der f 2*. Both allergens have been cloned and reveal over 85% to 90% sequence homology (126). Their structure is similar to an LPS-binding protein involved in activation of toll-like receptor 4, but the function appears to be unrelated (127).

Der p 3 and *Der f 3* are found primarily in fecal material from the house dust mites. *Der p 3* has been cloned (128), and enzymatic studies have demonstrated serine protease activities consistent with trypsin (129). *Der p 6, Der f 6,* and *Der p 9* have been described as serine proteases with activity similar to chymotrypsin (130–132). *Der p 4* and *Eur m 4* have been cloned and identified as α-amylases (133). Other dust mite allergens worth mentioning include some tropomyosins, e.g., *Der p 10* and *Der f 10,* which may cross-react with other tropomyosins that serve as major allergens in shellfish and invertebrates (134). In addition to group 1 and 2 allergens (*Der p 1/Der f 1; Der p 2/Der f 2*), it has also been recently proposed that group 23 allergens (*Der p 23*) are also deemed to be immunodominant in the hierarchy of IgE reactivity of dust mite allergens (135). A listing of house dust mite allergens by group number is shown in Table 6.4

(135).

There are other species of mites that are pests in areas of stored grain and can cause allergy, particularly in farm workers. Species include *Acarus siro, Tyrophagus putrescentiae, Lepidoglyphus* (*Glycyphagus*) *domesticus*, and *Lepidoglyphus destructor*. Spider mites (*Panonychus ulmi* and *Tetranychus urticae*) have been implicated in occupational allergy among apple farmers, and citrus red mite (*Panonychus citri*) among citrus farmers (136,137).

EPITHELIAL AND OTHER ANIMAL ALLERGENS

Animal allergens can be found in many types of tissues: hair, feathers, saliva, urine, and dander. *Dander* is the word for desquamated animal epithelium, which is shed constantly. People often believe that a short-haired or hairless animal is not allergenic, which is a common misconception.

The most severe symptoms tend to be in people allergic to cats. It is unknown whether this is because of the strength of the allergic reaction, the quantities in the air, or the size of the airborne particles. IgE to the major allergen, *Fel d 1*, is present in 80% of cat-sensitive individuals and has traditionally been thought to be the primary antigen responsible for allergic disease. *Fel d 1* is produced significantly in cat saliva and also found in the sebaceous glands of the skin (138) and is present on the fur of cats irrespective of the pet's licking tendencies. The *Fel d 1* molecule has some sequence homology with uteroglobin (139). Crystal structures of recombinant *Fel d 1* also have a significant resemblance to uteroglobin, which is cytokine-like molecule with anti-inflammatory and immunomodulatory properties (140). Recently, two additional major allergens have been identified using molecular techniques. *Fel d 3* (cystatin) has been identified, and appears to be a cysteine protease based on molecular modeling (141,142). *Fel d 4* has been suggested as a major allergen, and 47% of patients have a significantly higher IgE titer against *Fel d 4* than against *Fel d 1*. *Fel d 4* is a lipocalin that has sequence homology with other known animal allergens (143). The IUIS also recognizes *Fel d 5w* (a cat IgA), *Fel d 6w* (a cat IgM), *Fel d 7* (von Ebner gland protein), and *Fel d 8* (Latherin-like protein) as of this publication though the significance of these allergens are unclear (1).

TABLE 6.4 HOUSE DUST MITE ALLERGENS

Hierarchy of IgE reactivity of denominated *Dermatophagoides* house dust mite allergens (by group number)

Immunodominant	1 Cysteine protease
	2 ML domain
	23 Peritrophin-like[a]
Mid-tier	4 Amylase
	5 Unknown with coiled coil bundle structure
	7 LPS-binding/bactericidal/permeability-increasing protein-like
	21 Group 5 homologue (paralogue)
Minor	3 (trypsin), 6 (chymotrypsin), 8 (glutathione-S-transferase) 9 (collagenolytic serine protease), 10 (tropomyosin), 11 (paramyosin), 12 (not found in pyroglyphid mites), 13 (fatty acid binding protein), 15 (chitinase-like), 16 (gelsolin), 17 (EF-hand protein), 18 (inactive chitinase-like), 19 (not found in *Dermatophagoides*), 20 (arginine kinase)
Not determined (no gravimetric estimates of IgE binding to whole allergen or comparative titrations with known immunodominant allergens)	14 (large lipid transfer), 22 (ML-domain-like), 24 (ubiquinol-cytochrome c reductase), 25 (triosephosphate isomerase), 26 (myosin alkali light chain), 27 (serpin), 28 (heat shock protein 70), 29 (peptidyl-prolyl *cis-trans* isomerase/cyclophilin), 30 (ferritin heavy chain), 31 (cofilin), 32 (inorganic secreted pyrophosphatase), 33 (α-tubul in)

Cats have significant individual variation in the production of *Fel d 1*, with male cats generally producing greater amounts of allergen than females. The variability of *Fel d 3* and *Fel d 4* have not been studied. These factors may explain why some patients are more allergic to certain cats than to others.

Air sampling in rooms occupied by cats show abundant cell fragments <5 μm in diameter. Particles of this size are able to reach small bronchioles. The quantity of *Fel d 1* allergen detected in room air is similar to the quantity required to cause a 20% decrease in forced expiratory volume in 1 s (FEV_1) on pulmonary function in conventional bronchoprovocation testing (approximately 0.09 μg/mL) (144). The small particle size may also explain why cat allergen can remain airborne in undisturbed conditions for extended periods. Further studies have indicated that it takes up to 24 weeks after removing a cat from inside the home to get back to the baseline quantity of *Fel d 1* found in a home with no cat (145). It has been shown that repeated washing of the pet does help to reduce the release of cat allergens though the effect appears to last about 1 week necessitating frequent washing (146,147).

Dog allergens can be found in dander, saliva, urine, and serum. Seven allergens have been described and recognized by the IUIS as of this chapter iteration, *Can f 1–7*. Four of the allergens, *Can f 1, Can f 2, Can f 4*, and *Can f 6*, are lipocalins with dimeric structures (1). *Can f 1* is ubiquitous in homes with dogs while also being detected in a third of the homes without dogs. IgE antibodies to *Can f 1* can be seen in 50% to 90% of subjects sensitized to dog, whereas 25% to 33% of patients react to *Can f 2* (148). Sera from albumin-sensitive patients have a high cross-reactivity with cat and other animal albumins (149). There is also evidence that *Can f 6* cross-reacts with *Fel d 4* in cats and *Equ c 1* in horses (150,151). Dander from all breeds is allergenic, including poodle, but differences between breeds occur in the number and quantity of antigens (152). Individual patients vary in their skin test results to different dog breeds, but in one study these variations did not correlate with the patient perception of specific breed allergy (153).

Many patients, who are sensitive to animals, are also sensitive to other perennial allergens, which complicates the determination of which allergen is responsible for their symptoms. Patients often have difficulty accepting that a pet

is causing their symptoms, even with a positive skin test. Cat allergen can persist in the environment for 6 months after a pet is removed. For this reason, moving a pet from the house is not a good indicator. It is necessary for the patient to be removed to another environment to determine the role of the animal.

Horse allergy can cause severe symptoms, similar to the symptoms seen with cat allergy, though it is typically easier to manage because the horses do not live in the house. Some antigens are common to horse dander and serum, creating the potential for a serious problem in patients when horse serum (such as an antivenom) may be urgently needed. Four horse allergens have been identified so far. *Equ c 1* and *Equ c 2* have been cloned and both described as members of the lipocalin family (154,155), while *Equ c 3* is an albumin and *Equ c 4* is a latherin (Table 6.5). Nearly three-fourths of patients allergic to horse have IgE antibody to *Equ c 1*, the immunodominant horse allergen (156). Allergy to cows, goats, and sheep is primarily found in farmers.

Mouse and rat allergy are significant problems for laboratory workers and for people living in the inner city (157,158). In most mouse-sensitive subjects, a major urinary protein, *Mus m 1*, is a significant allergen. It is also a lipocalin and has sequence homology with *Can f 2* (159). The primary rat urinary allergen is *Rat n 1*, which is also a lipocalin/α-2u-globulin. In one study, rat sebaceous glands were not found to be the source of allergenic secretions (160), but other studies have reported a high-molecular-weight protein (>200 kDa), which was believed to originate from rat sebaceous glands (161). Several occupational issues exist for laboratory workers. Feeding and cleaning rats produce the highest airborne concentrations of the prealbumin protein *Rat n 1* (162). Using ventilated cages and negative air pressure appears to reduce exposure to mouse allergens (163). Many companies prefer to screen patients for atopy prior to employment. There is some controversy over the predictive value of atopy in determining whether someone will develop occupational animal allergy (164,165). A listing of common animal allergens is shown in Table 6.5.

INSECTS

Cockroach infestation is greater in the inner cities and in southern climates, though it can occur in northern climates as well. Cockroach allergens have been shown to be a cause of allergic asthma using RASTs and bronchoprovocation studies.

The two most common indoor species of cockroaches are *Blattella germanica* (German cockroach) and *Periplaneta americana* (American cockroach).

Immunoelectrophoretic studies of roach allergens suggest that most allergens are present in the whole-body and cast-skin fractions, with feces and egg casings less allergenic. Approximately 10 allergens have been described for the German cockroach and nine have been recognized by the IUIS (Table 6.6) for the American cockroach (166). *Per a 1* and *Bla g 1* are cross-reactive and have sequence homology with a mosquito digestive protein (167). Cockroaches that eat less food secrete less of this allergen (168). *Bla g 2* shows sequence homology to an aspartic protease but shows weak activity (169). Cockroaches secrete more of this allergen when exposed to sublethal concentrations of boric acid (170). *Per a 3* has been defined and may have some cross-reactivity with a German cockroach allergen (171). *Bla g 4* is a ligand-binding protein belonging to the calycin family (166). *Bla g 5* is a glutathione-*S*-transferase (172). In addition, a tropomyosin (*Per a 7*) has been identified as an allergen from *P. americana*, with sequence homology to dust mite and shrimp tropomyosins (173); it reduces the production of IL-12 and expression of TLR-9 (166). Cockroach mitigation strategies include sealing points of entry into the house and kitchen, storage of food sources in enclosed containers, general house-cleaning, and poison bait. Relevant practice parameters were published in 2013 (174).

Moth allergy has been found in considerable frequency in some studies. In Minnesota, the moth *Pseudaletia unipuncta* (Haworth) appears to be a significant outdoor allergen with outdoor levels similar to pollens. The allergen peaks in June and again in August to September. Of patients with other positive skin tests, 45% reacted to whole body extract of the moth (175). In Japan, 50% of asthmatics have sensitivity to the silkworm moth (*Bombyx mori*) (176). They appear to cross-react with butterfly allergens on RAST inhibition studies, but not with mites (176). Finished silk products generally are not allergenic, but quilts that are stuffed with silk may contribute to asthma and rhinitis.

TABLE 6.5 ANIMAL ALLERGENS

PURIFIED AND CHARACTERIZED ANIMAL ALLERGENS[a]

ANIMAL	MAJOR ALLERGEN[b]	OTHER ALLERGENS
Cat	Fel d 1 (uteroglobin)	Fel d 2 (albumin)[c]
	14 + 4 kDa	Fel d 4 (lipocalin)

		Fel d 7 (VEGP)[d]
		Fel d 3 (cystatin)
		Fel d 5w (cat IgA)[e]
		Fel d 8 (latherin-like)
Dog	Can f 1 (lipocalin)	Can f 2 (lipocalin)
	23–25 kDa	Can f 4 (lipocalin)
		Can f 6 (lipocalin)
		Can f 3 (albumin)[c]
		Can f 5 (arginine esterase)[f]
Guinea pig	Cav p 1 (lipocalin)	Cav p 3 (lipocalin)
	20 kDa	Cav p 4 (albumin)
	Cav p 2 (lipocalin)	
	17 kDa	
Horse	Equ c 1 (lipocalin)	Equ c 2 (lipocalin)
	25 kDa	Equ c 4 (latherin)
		Equ c 3 (albumin)[c]

Mouse	Mus m 1 (lipocalin; urinary prealbumin)	
	17 kDa	
Rat	Rat n 1 (lipocalin; α-2u-globulin)	
	17 kDa	
Rabbit	Ory c 1 (lipocalin)	Ory c 3 (lipophilin)
	17–18 kDa	19–21 kDa

[a]Component-specific IgE levels can be measured with component-specific IgE assays or by using the Immuno Solid-phase Allergen Chip (ISAC Thermo Fisher Scientific, Uppsala, Sweden).

[b]Airborne measurements of each allergen source have been based on the major allergen.

[c]Albumins have molecular weights of 67 to 69 kDa and can cross-react extensively.

[d]von Ebner gland protein.

[e]The main epitope on cat IgA and also on cat IgM is the oligosaccharide α-gal.

[f]This molecule is a kallikrein.

From Konradsen JR, Fujisawa T, van Hage M, et al. Allergy to furry animals: new insights, diagnostic approaches, and challenges. *J Allergy Clin Immunol*. 2015;135(3):616–625.

Asian lady-beetle infestation of homes appears to be an allergen in multiple regions of the United States (177). Mayfly, house fly, and caddis fly sensitization has been reported in significant numbers (178), particularly in the Great Lakes region around Lake Erie given that their life cycle has an aquatic larval stage. In the Sudan, inhalation of the allergens from the "green nimmiti midge" has been associated with seasonal allergies, apparently a reaction to the hemoglobin molecule (179). Some insects are used as food or bait and can cause allergy for the people using them. Crickets used for frog food, chironomid larvae used for fish food, or mealworms (*Tenebrio molitor*) used as fishing bait or reptile food have all been demonstrated to be significant allergens for some hobbyists (180–182). Some locusts have also been a source of occupational allergy

including the common housefly (*Musca domestica*) and the grain beetle (*Alphitobius diaperinus*) (183,184). Many biting and stinging insects also elicit both immediate and delayed hypersensitivity reactions via their salivary secretions. These include mosquitoes, fleas, sand flies, deer flies, horse flies, and Tsetse flies. While the skin reactions to these biting insects are partly being mediated by the relative toxicity of their secretions, there does appear to be the presence of specific IgE to some of the major allergens (particularly southern house mosquito—*Culex quinquefasciatus*) that is contributing to such hypersensitivities. Immunotherapy with mosquito extract appeared to improve rhinitis and asthma symptom scores in one study (185). Hymenoptera venom hypersensitivity reactions are the subject of Chapter 15 in this text and not addressed here.

TABLE 6.6 COCKROACH ALLERGENS

ALLERGEN	M.W.[a]	FUNCTION/HOMOLOGY	IgE PREVALENCE	MAJOR LINEAR IgE EPITOPES	GENEBANK ACCESSION #
Bla g 1	46	• Lipids-associated and/or binding protein (118) (i.e., palmitic, oleic, and steric acids) • Nonspecific transport of lipid molecules in cockroach • Non-enzymatically active aspartic protease (34,40,119)	20%–40%	a.a. 1–111, 289–403, and 394–491 (32)	AF072219 AF072221 L47595 AF072220
Bla g 2	36	• Glycoprotein, decorated glycans indicated to be important for IgE binding (55,73) • Binds to human β-defensin 3 (44)	40%–70%	a.a. 1–75 and 146–225 (45)	U28863
Bla g 3	79[a]	• Homologous hemocyanin and American cockroach	n.r.	n.r.	GU086323

		•	allergen Per a 3 (120)		
Bla g 4	21	•	Ligand binding protein, members of the calycin protein family (121)	17%–40%	a.a. 34–73, 78–113, and 118–152 (34)	U40767
Bla g 5	23	•	Sigma class glutathione-*S*-transferase (35,36,122)	35%–68%	a.a. 176–200 (37)	U92412
Bla g 6	21	•	Homologous to muscle protein troponin C with four calcium-binding domains (35)	14%	Dependent upon calcium level, a.a. 96–151 (123)	DQ279092 DQ279093 DQ279094
Bla g 7	31	•	German cockroach tropomyosin (124)	18%	n.r.	AF260897
		•	Can induce TIM4, CD80, and CD86 and increased IL-13 secretion in human DCs (125)			
		•	Potential involvement in DCs-induced T_H2 polarization (47)			
Bla g 8	n.r.	•	Calcium binding protein	n.r.	n.r.	DQ389157
		•	Myosin light chain (47)			
Bla g 11	57	•	α-Amylase			DQ355516 KC207403
Per a 1	45	•	Homologous to the mosquito precursor	9%–100%	a.a. 358–446 (38)	AF072222 U78970

		•	protein, ANG12, which may be involved in digestion (123)		U69957 U69261 U69260
Per a 2	42	•	Inactive aspartic protease-like (126)	81%	a.a. 57–86, 200–211, and 299–309 (17)	GU188391
		•	42%–44% homology to Bla g 2			
Per a 3	72	•	Homologous to insect hemolymph proteins, arylphorin/hemocyanin (127)	26%–95%	a.a. 400–409, 466–471, 580–595, and 595–605 (39)	L40818 L40820 L40819 L40821
Per a 5[b]	25	•	Glutathione-*S*-transferase (128)	25%	n.r.	AY563004
Per a 6	17	•	Homologous to insect troponin Cs and vertebrate calmodulins (129)	14%	n.r.	AY792950
Per a 7	33	•	Tropomyosin (123)	13%–54%	n.r.	Y14854 AF106961
		•	Induce reduction of IL-12 production and expression of TLR9 in P815 mastocytoma cells (130)			
Per a 9	43	•	Arginine kinase (51)	80%–100%	p. LTPCRNK	AY563004
Per a 10	28	•	Serine protease and insect trypsins (131)	82%	n.r.	AY792954
Per a 11	55	•	α-Amylase (132)	83%	n.r.	n.r.
Per a 12	45	•	Chitinase (133)	64%	n.r.	n.r.

AIR POLLUTANTS AND CHEMICALS

Many patients report that their asthma or rhinitis is made worse by airborne pollution, second-hand smoke, chemical irritant, or strong fragrances. Air pollution appears to have an impact on asthma and rhinitis. Multiple epidemiologic studies have demonstrated a correlation between levels of common outdoor air pollutants and hospital admissions or emergency room visits (186,187). However, these epidemiologic studies are limited by confounding factors, including air temperature and levels of other outdoor aeroallergens. For this reason, experiments also have been performed under controlled conditions involving short exposures to individual pollutants.

Ozone is generated by the action of ultraviolet light on precursor pollutants such as nitrogen dioxide (NO_2), hydrocarbons from sources like automobiles and power plants. Ozone causes decreased FEV_1 and forced vital capacity as well as increases in bronchial hyperresponsiveness in both asthmatics and non-asthmatics at concentrations as low as the National Ambient Air Quality Standard of 0.12 ppm (186) and causes epithelial damage resulting in increased inflammatory cells and mediators (IL-6, IL-8, GM-CSF, and fibronectin) in the nasal and bronchoalveolar lavage (188,189). A few bronchoprovocation studies have suggested that ozone increases the respiratory response to allergen (190,191). Ozone is a highly reactive oxygen intermediate, and people with a genetic defect in glutathione reduction appear to be more susceptible to its effects (192). NO_2 from car emissions also may play a role and serve as a precursor for smog, although the evidence in controlled exposures is less convincing than for ozone (193). NO_2 is also responsible for increased emergency room visits and wheezing and rescue medication use among asthmatic children and also amplifies the allergenic response to other inhaled allergens (189).

Diesel exhaust particles (DEPs) also have been implicated in allergic disease. When they are given in combination with an allergen, they promote both allergen-specific IgE production and a T_H2 cytokine profile (194). One study

attempted to sensitize atopic individuals to keyhole limpet hemocyanin, a protein isolated from a marine mollusk, with no known cross-reactive antibodies in humans. Exposure to this allergen with DEPs generated a specific IgE response, whereas exposure to the allergen alone did not (195). DEPs comprise the majority (>90%) of particulate matter (fine and ultrafine particles) that is found in the world's largest cities leading to higher overall PM_{10} levels, particulate matter 10 µm or less, which in turn have been associated with early onset exacerbations in asthmatic children (189).

Sulfur dioxide is a product of soft coal burned for industrial use and promotes airway inflammation, eosinophilia, airway hyperresponsiveness, and fibrosis (196). A recent study demonstrated that even short-term exposure leads to increased emergency room visits and hospitalizations (197). Metabisulfites, sulfiting agents used as preservatives agents, may also be a respiratory irritant (198). Carbon monoxide (CO) impairs oxygen transport, which is only likely to be important for the individual with low respiratory reserve. One recent study published indicated that higher exposure to CO during infancy increased the risk of inception of allergic rhinitis while the risk of ongoing eczema symptoms increased in children who had increased CO exposure in the previous year (199).

Formaldehyde is released into the air from particle board, foam insulation, furnishings, tobacco smoke, and gas stoves. Symptoms are often most prominent for people in mobile homes, where large amounts of particle board have been used in a relatively small enclosed space. Symptoms may start after exposure to as low as 1 ppm in some individuals and is still thought to be irritative, not allergenic. One recent publication posits that formaldehyde induces airway hyper-responsiveness via Rho-kinase dependent calcium sensitization pathways in human airway smooth muscle cells (200).

The term *sick building syndrome* is used to describe symptoms that happen to multiple people in the same building during a similar time frame. Buildings with this problem tend to have less air exchange with the outdoors and less efficient filtrations systems. Conjunctival and respiratory tract symptoms are most common but are often accompanied by nonspecific complaints, such as headache, fatigue, and inability to concentrate. Mechanisms are usually not allergic and determination of specific irritants is very difficult in a clinical setting. Formaldehyde and second-hand smoke are among the most common associations. Sometimes contamination of the ventilation system with mold can generate allergic reactions or even hypersensitivity pneumonitis. A psychogenic cause of the sick building symptoms should be considered but not assumed.

Symptoms usually improve when the ventilation problems are corrected (201).

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Airborne Pollen Prevalence in the United States

ESTELLE LEVETIN

The dramatic seasonal appearance of windborne pollen and resulting symptoms are events familiar to physicians and laypersons alike. By knowing where and when symptoms occur annually, the informed allergist can focus on probable offenders with some confidence. Therefore, appreciating patterns of pollen prevalence confers an important advantage in providing informed patient care.

Unfortunately, dependable information on the prevalence of airborne pollen across the United States remains incomplete. The National Allergy Bureau (NAB) of the American Academy of Allergy, Asthma, and Immunology consists of a network of 85 accredited volumetric sampling stations in the United States and Canada. NAB stations provide data on pollen levels, which are readily available on the Internet (pollen.aaaai.org). Member stations are not uniformly distributed, and many states, especially in the west, lack an NAB station, and other states have only a single reporting station. In addition, some city or county public health agencies routinely conduct air sampling and make the data publicly available, and some clinicians, not affiliated with the NAB, also run pollen sampling stations. Beyond this, there is limited reliable information on airborne pollen prevalence.

An allergist moving to an unfamiliar area needs to obtain or, more often, generate the information on which he or she will rely. Available information is not always easy to interpret and may reflect "conventional wisdom" (and practice) or skin test surveys rather than air sampling data. Even when aerobiologic data are available, standard microscope analysis of air samples can provide only the genus or plant family for most pollen types, e.g., oak and grass pollen. Molecular or immunologic analyses are necessary for species-level identification from air samples, and these are not routinely performed (1–4). In addition, bioaerosols smaller than intact grains may carry pollen allergens, and their potential for travel without microscopic detection is obvious (5,6). This

often leaves determination of source species to published field surveys, which may not be routinely updated; considering this, gaps in the species listed in this chapter are inevitable. Local botanists and plant ecologists can often be a valuable resource for obtaining information on area vegetation (7). Additional data on plant distribution are currently available on several websites, including The Biota of North America Program: North American Vascular Flora (www.bonap.org) and United States Department of Agriculture Plants Database (plants.usda.gov). Both are searchable databases providing state- and sometimes county-level plant distribution maps. While providing information on the distribution of native plants, these sites lack information on their allergenic importance.

Much of the appeal of North America's landscape arises from its climatic, and floristic, diversity. This variety provides inherent challenges for the allergist, especially because plant growth and land use rarely conform to state boundaries. Even regional groupings, as provided here, must be qualified for marked local climatic differences arising from effects of mountain ranges, upwind bodies of water, or other geographic features that may influence plant distribution.

Although previously published pollen data are often treated as an unchanging description of the local aerobiology, there is little to justify such optimism. Local plantings of crops such as sugar beets, pecans, or olives may displace native plant populations (8). In addition, long-distance transport is known to carry pollen into regions where the species does not grow or to introduce the pollen before local populations have started to shed pollen. Long-distance transport has been well documented and may be more common and/or extensive than suspected. The transport of mountain cedar (*Juniperus ashei*) pollen from central Texas and southern Oklahoma to Tulsa, Oklahoma, and other areas has been extensively studied (9–11). In fact, the transport of this pollen into Ontario, Canada, has also been documented (12,13). Other well-known examples of long-distance transport include the transport of *Ambrosia* (ragweed) pollen in central and eastern Europe (14,15) and the preseason transport of *Betula* (birch) pollen in northern Europe (16).

Land-use practices may modify pollen exposure patterns indirectly as well as by directly providing source species. Species of ragweed, for example, selectively colonize cultivated fields, disturbed areas, and roadsides. It is not unusual to find ragweed proliferating along roadsides, especially along the margins of winter-salted roads that are overgrown rapidly the following summer (17,18).

Changes in pollen prevalence over several decades can be attributed to many factors as diverse as extensive street tree planting with allergenic species (8,19), reforestation (planned or as natural succession), and range extension by opportunistic species, e.g., mugwort in northeastern states (20) and eastern red cedar in the Central Plains (21). The last of these effects deserves special attention in a setting of climate change.

The influence of climate change on environmental allergens and allergic disease has been the focus of numerous studies and reviews (22–25). Warmer temperatures have led to distribution changes for many species in recent decades. These may be latitudinal or altitudinal shifts, with some species showing range contraction and others showing expansion (22,26). Warmer winter temperatures in many areas have resulted in a trend toward an earlier annual appearance of many spring tree-pollen types in northern areas of both North America and Europe (22–24,27). There has also been a trend toward a longer season for ragweed pollen in the fall in northern areas of the United States and Canada (28). Research has also shown that many species, including *Ambrosia* (29–31), *Artemesia* (32), *Betula* (33), and *Phleum* (34), increased growth, biomass production, flowering, or pollen production under experimental conditions of elevated carbon dioxide.

Similarities and cross-reactivity among pollen allergens of some related taxa have been well described, and these have an obvious impact on patient care. Efforts to prioritize the clinical impact of pollen types also reflect a growing economic imperative to avoid "duplication" among allergens employed for diagnosis and treatment. Guidelines for immunotherapy have reflected these concerns in the search for minimally adequate allergen panels (35,36). The Betulaceae (birch family) offer perhaps the best-documented example of shared pollen components among genera with major allergens of prominent birch, alder, and hazelnut species essentially interchangeable immunochemically (37). Another important source of cross-reactivity can be found within the Cupressaceae (cypress family) among pollen allergens of cedar, juniper, and cypress (38). Additional information on cross-reactive allergens can be found in the previous chapter (39) as well as recent reviews (40–42). However, since pollen emissions of related taxa are often microscopically indistinguishable, field surveys and known patterns of allergen content still remain key in choosing materials for clinical use.

Despite the aforementioned reservations, this chapter attempts to list clinically significant sources of airborne pollen. The most common genera of

hay-fever trees and weeds in the United States are listed in Table 7.1 along with their common names; Tables 7.2 to 7.9 present the plants on a state-by-state basis along with their approximate periods of peak pollen prevalence. Where reference to two or more species of a single genus is intended, spp. is used after the generic name; sp. designates an uncertain species in a stated genus. Relative importance is implied by a three-level scale: + + +, generally quite important; + +, of secondary importance; +, occasionally or locally worth considering. Finally, cardinal directions, abbreviated as N, S, E, W, and L (for local occurrence), should pose no problem. Major sources of airborne pollen for each state or group are listed in the order: trees, grasses, weeds (i.e., broad-leaved, nonwoody plants, or "forbs"). Within each of these categories, plants are listed by months of pollen prevalence.

TABLE 7.1 MAJOR NORTH AMERICAN WINDBORNE TREE AND WEED POLLEN SOURCES AND THEIR GENERIC (LATIN) NAMES

COMMON NAME	LATIN GENUS	COMMON NAME	LATIN GENUS
Alder	*Alnus*	Mesquite	*Prosopis*
Amaranth	*Amaranthus*	Mountain cedar	*Juniperus*
Ash	*Fraxinus*	Mugwort	*Artemisia*
Aspen	*Populus*	Mulberry	*Morus*
Beech	*Fagus*	Oak	*Quercus*
Birch	*Betula*	Pecan	*Carya*
Butternut	*Juglans*	Pigweed	*Amaranthus*
Cottonwood	*Populus*	Plantain	*Plantago*
Dock	*Rumex*	Ragweed	*Ambrosia*

Elm	*Ulmus*	Red cedar	*Juniperus*
Hackberry	*Celtis*	Sage	*Artemisia*
Hickory	*Carya*	Sorrel	*Rumex*
Juniper	*Juniperus*	Sweet gum	*Liquidambar*
Lamb's quarter	*Chenopodium*	Sycamore	*Platanus*
Maple	*Acer*	Walnut	*Juglans*
Marsh elder	*Iva*	Willow	*Salix*

TABLE 7.2 MAJOR SOURCES OF WINDBORNE POLLEN IN THE NORTHEAST

THE NORTHEAST[a]

Connecticut and New York

Delaware and New Jersey

Massachusetts and Rhode Island

Pennsylvania, Maryland, District of Columbia, and West Virginia

Maine, New Hampshire, and Vermont

POLLEN TYPE	GENUS AND SPECIES	IMPACT	PREVALENCE
Connecticut and New York			

Trees

Juniper, yew	*Juniperus* spp., *Taxus* spp.	+	Mar–Apr
Alder	*Alnus* spp.	+(L)	Mar–Apr
Elm, American	*Ulmus americana*	++	Apr
Birch, gray, red, etc.	*Betula* spp.	+	Apr
Cottonwood	*Populus deltoides*	++	Apr
Maple, sugar, red	*Acer saccharum, A. rubrum*	+	Apr–May
Ash, white	*Fraxinus americana*	+	Apr–May
Oak, white, red	*Quercus alba, Q. rubra*	+++	Apr–May
Hickory	*Carya ovata, Carya* spp.	+	May
Beech	*Fagus grandifolia*	++(L)	May
Hackberry (SE)	*Celtis occidentalis*	+(L)	May–June
Mulberry, red, black (L)	*Morus rubrum, M. nigra*	+	May

Grasses

June/blue	*Poa pratensis*	+++	May–July
Orchard	*Dactylis glomerata*	+++	May–July
Timothy	*Phleum pratense*	+++	June–July

Red top	*Agrostis alba*	+	May–July
Ryegrass	*Lolium* spp.	+	June–July
Sweet vernal	*Anthoxanthum odoratum*	++	May–July
Weeds			
Sorrel; dock	*Rumex acetosella, Rumex* spp.	+	May–June
Ragweed, short	*Ambrosia artemisiifolia*	+++	Aug–Sep
Ragweed, giant	*Ambrosia trifida*	+	Aug-Sep
Plantain, English	*Plantago lanceolata*	+	June–Sep
Lamb's quarters	*Chenopodium album*	+	Aug–Sep
Pigweed, amaranths	*Amaranthus* spp.	+	Aug–Sep
Mugwort	*Artemisia vulgaris*	+(L)	Aug–Sep

Sweet fern (*Myrica asplenifolia*) and bayberry (*M. caroliniana*) of sandy soils are modest local factors in pollinosis.

Delaware and New Jersey

Trees			
Red cedar	*Juniperus virginiana*	+	Mar–Apr
Alder	*Alnus* spp.	+(L)	Mar–Apr

Elm, American	*Ulmus americana*	++	Apr
Birch, gray, red, etc.	*Betula alba, B. nigra, Betula* spp.	+	Apr
Cottonwood	*Populus deltoides*	+	Apr
Red maple	*Acer rubrum*	+	Apr
Ash, white	*Fraxinus americana*	++	Apr–May
Sycamore, eastern, hybrids	*Platanus* spp.	+	Apr–May
Oak, white, red, etc.	*Quercus* spp.	+++	Apr–May
Beech	*Fagus grandifolia*	+(N)	May
Walnut, black	*Juglans nigra*	+(L)	May
Hickory	*Carya* spp.	+	May
Sweet gum	*Liquidamber styraciflua*	+(S)	May
Mulberry	*Morus* spp.	+(L)	May

Grasses

Strongly similar to Connecticut and New York. In addition, Bermuda grass occurs in more southern areas. Others, including fescue (*Festuca elatior, Festuca* spp.) are marginal, local sources; velvet grass (*Holcus lanatus*), Johnson grass (*Sorghum halepense*), and others may evoke symptoms locally.

Weeds

Closely similar to Connecticut and New York. In addition, yellow dock (*Rumex crispus*) may contribute in June, but mugwort is less prominent.

Massachusetts and Rhode Island

Trees

Red cedar	*Juniperus virginiana*	+	Mar–Apr
Elm, American	*Ulmus americana*	+	Apr
Poplar, aspen(s)	*Populus* spp.	+	Apr
Willow, black	*Salix nigra*	+	Apr–June
Ash, white	*Fraxinus americana*	+	Apr–May
Birch, yellow, paper	*Betula alleghaniensis, B. papyrifera*	+++	Apr–May
Birch, gray	*Betula populifolia*	+	Apr-May
Maple, sugar	*Acer saccharum*	++	Apr–May
Oak, white, red	*Quercus alba, Q. rubra*	+++	May
Beech	*Fagus grandifolia*	+	May
Mulberry, red, black (L)	*Morus rubra, M. nigra*	+(L)	May
Hemlock	*Tsuga canadensis*	+(W)	May

Grasses

Strongly similar to Connecticut and New York.

Weeds

Strongly similar to Connecticut and New York. Mugwort (*Artemisia vulgaris*) is found increasingly in the east and merits clinical concern.

Pennsylvania, Maryland, District of Columbia, and West Virginia

Trees

Elm, American	*Ulmus americana*	+	Mar–Apr
Birch, yellow	*Betula alleghaniensis*	++	Apr
Maple, red	*Acer rubrum*	+	Apr
Cottonwood, aspen	*Populus* spp.	+	Apr
Ash, white	*Fraxinus americana*	++	Apr
Sycamore	*Platanus* spp.	+	Apr–May
Oak, white, red, etc.	*Quercus* spp.	+++	Apr–May
Hickory	*Carya* spp.	+	Apr–May
Walnut, butternut	*Juglans* spp.	+(L)	Apr–May
Sweet gum	*Liquidamber styraciflua*	+	Apr–May

Mulberry, red, black (L)	*Morus rubra, M. nigra*	+	May

Grasses

June (blue), orchard, timothy, and ryegrasses produce abundant late May to late July pollen. Bermuda grass appears also in Maryland, District of Columbia, and West Virginia.

Weeds

Strongly similar to Connecticut and New York.

Maine, New Hampshire, and Vermont

Trees

Elm, American	*Ulmus americana*	+	Apr
Ash, white	*Fraxinus americana*	+	May
Birch, yellow, paper, etc.	*Betula lutea, B. papyrifera, Betula* spp.	++	Apr–May
Aspen, cottonwood, poplar	*Populus tremuloides, P. grandidentata, P. deltoides, P. balsamifera (N)*	++	Apr–May
Oak, red, white	*Quercus rubra, Q. alba*	++	May
Maple, sugar	*Acer saccharum*	++	May
Beech	*Fagus grandifolia*	+	May

Hickory	*Carya* spp.	+(S)	May

Grasses

Strongly similar to Connecticut and New York; May–July period shortens to the north.

Weeds

Sorrel, docks	*Rumex* spp.	+	May–June
Ragweed, short	*Ambrosia artemisiifolia*	+++	Aug–Sep
Lamb's quarters	*Chenopodium album*	+	July–Sep
Pigweed, redroot	*Amaranthys retroflexus*	+	July–Sep
Plantain, English	*Plantago lanceolata*	+	June–Aug
Mugwort	*Artemisia vulgaris*	+(SE)	Aug

[a]As the area longest intensively colonized by Europeans, the paradigm of a brief hectic spring tree pollen season, grass pollen from late May to July, and the ragweed onslaught in late summer originated here. Despite their size, metropolitan areas receive ample pollen from upwind sources and occasionally from urban planting of ash, oak, sycamore, and other trees. Traditional havens from ragweed exposure in northern states today offer minimal protection, at best. Ryegrass-related northern grass species predominate, with Bermuda grass appearing only in the southernmost tier.

TABLE 7.3 MAJOR SOURCES OF WINDBORNE POLLEN IN THE SOUTHEAST

THE SOUTHEAST[a]

Kentucky and Tennessee

North Carolina and Virginia

Georgia, South Carolina, Alabama, and Mississippi

Arkansas and Louisiana

Florida

POLLEN TYPE	GENUS AND SPECIES	IMPACT	PREVALENCE
Kentucky and Tennessee			
Trees			
Elm, American, slippery, etc.	*Ulmus americana, U. rubra, Ulmus* spp.	+	Feb–Mar
Red cedar	*Juniperus virginiana*	+(W)	Feb–Mar
Ash, white, green	*Fraxinus americana, F. pennsylvanica*	++	Mar–May
Red maple	*Acer rubrum*	+	Feb–Mar
Oak, red, white, other	*Quercus* spp.	+++	Mar–Apr
Hornbeam, American	*Carpinus caroliniana*	+(L)	Mar–Apr
Birch, sweet, yellow	*Betula lenta, B. alleghaniensis*	+(L)	Mar–Apr
Sweet gum	*Liquidamber styraciflua*	+	Apr
Cottonwood	*Populus deltoides*	++	Mar–Apr

Hickory, pecan	*Carya* spp.	+++	Apr–May
Sycamore	*Platanus occidentalis*	+	Apr–May
Mulberry, red	*Morus rubra*	+	Apr–May
Walnut, butternut	*Juglans* spp.	+	Apr–May
Grasses			
June (blue)	*Poa pratensis*	+++	Apr–Sep
Timothy	*Phleum pratense*	+++	May–July
Orchard	*Dactyis glomerata*	++	May–June
Bermuda	*Cynodon dactylon*	+++	May–Sep
Red top	*Agrostis alba*	+	May–July
Johnson	*Sorghum halepense*	+	June–Sep
Weeds			
Sorrel, dock	*Rumex* spp.	+	Apr–June
Plantain, English	*Plantago lanceolata*	+	May–Aug
Amaranths, pigweed	*Amaranthus* spp.	+	July–Sep
Burning bush	*Kochia scoparia*	+	July–Sep
Ragweed, short, giant	*Ambrosia artemisiifolia, A.*	+++	Aug–Sep

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	trifida		
Burweed marsh elder	*Iva xanthifolia*	+(W)	Aug–Sep

North Carolina and Virginia

Trees

Alder, hazel	*Alnus serrulata*	+	Feb–Mar
Elm, American, slippery	*Ulmus americana, U. rubra*	+	Feb–Apr
Maple, red	*Acer rubrum*	++	Feb–Apr
Ash, white, green	*Fraxinus americana, F. pennsylvanica*	+	Feb–Apr
Oak, red, white, live[b]	*Quercus* spp.	+++	Mar–May
Sycamore	*Platanus occidentalis*	+	Apr–May
Hickory, pecan	*Carya* spp.	+++	Apr–May
Willow, black, etc.	*Salix nigra, Salix* spp.	+	Apr–May
Sweet gum	*Liquidamber styraciflua*	+	Apr–May
Hackberry	*Celtis laevigata*	+(S)	Apr–May
Bayberry	*Myrica* spp.	+(L)	Apr–May

Grasses

Strongly similar to Kentucky and Tennessee, although Bermuda grass is an incrementally dominant offender.

Weeds

Strongly similar to Kentucky and Tennessee

Georgia, South Carolina, Alabama, and Mississippi

Trees

Red cedar	*Juniperus virginiana*	+	Jan–Feb
Cottonwood	*Populus deltoides*	+	Feb–Mar
Elm, American, slippery	*Ulmus americana, U. rubra*	+	Feb–Mar
Maple, red	*Acer rubrum*	+++	Mar–Apr
Birch, river	*Betula nigra*	+	Mar–Apr
Mulberry	*Morus* spp.	+	Mar–Apr
Ash, white, green, etc.	*Fraxinus* spp.	+	Apr
Oak, red, white, live	*Quercus* spp.	+++	Feb–Mar
Hickory, pecan	*Carya* spp.	+++	Apr–May
Sweet gum	*Liquidamber styraciflua*	+	Mar–Apr
Bayberry	*Myrica* spp.	+(E)	Apr–May

Sugar (hack) berry	*Celtis laevigata*	++(L)	Apr–May

Grasses

Bermuda	*Cynodon dactylon*	+++	May–Oct
June (blue)	*Poa pratensis*	++	Apr–July
Johnson	*Sorghum halepense*	++	May–Oct
Ryegrass	*Lolium* spp.	+	May–July

Weeds

Sorrel, dock	*Rumex* spp.	+(N)	Apr–June
Ragweed, short, giant	*Ambrosia artemisiifolia, A. trifida*	+++	Aug–Oct
Pigweed, amaranths	*Amaranthus* spp.	+	May–Sep
Plantain, English	*Plantago lanceolata*	+	Apr–Oct
Nettle	*Urtica* spp.	+	July–Oct
Marsh elder, rough	*Iva ciliata*	+(W)	July–Oct

Arkansas and Louisiana

Trees

Juniper, cedar	*Juniperus* spp.	+++	Dec–Mar

Elm	*Ulmus* spp.	+	Jan–Mar
Sugar (hack) berry	*Celtis laevigata*	++	Mar–May
Oak, white, red	*Quercus* spp.	+++	Mar–Apr
Oak, live[b]	*Quercus virginiana*	++(S)	Mar–Apr
Mulberry, red	*Morus rubra*	+	Mar–Apr
Hickory, pecan	*Carya* spp.	+++	Apr–May
River birch	*Betula nigra*	+	Mar–Apr
Sweet gum	*Liquidamber styraciflua*	+	Apr–May
Grasses			
Bermuda	*Cynodon dactylon*	+++	Apr–Nov
June (blue)	*Poa* spp.	++	Apr–Nov
Johnson	*Sorghum halepense*	+	Apr–Nov
Ryegrass	*Lolium* spp.	+	May–Nov
Weeds			
Ragweed, giant, short	*Ambrosia trifida, A. artemisiifolia*	+++	Aug–Oct
Marsh elder, rough	*Iva ciliata*	+++	Aug–Oct
Western water hemp	*Acnida tamarascina*	++	July–Sep

Russian thistle	*Salsola pestifer*	+	June–Sep
Pigweed, amaranths	*Amaranthus* spp.	+	June–Sep

Florida[c]

Trees

Alder	*Alnus serrulata*	+(N)	Dec–Feb
Elm, American, etc.	*Ulmus americana, Ulmus* spp.	+(N)	Jan–Mar
Maple, red	*Acer rubrum*	+(N)	Jan–Feb
Juniper, cedar	*Juniperus* spp.	++	Jan–Mar
Bald cypress	*Taxodium distichum*	+++	Jan–Apr
Box elder	*Acer negundo*	++(N)	Feb–Mar
Sweet gum	*Liquidamber styraciflua*	+(L)	Feb–Mar
Oak, red (N), live, laurel	*Quercus rubra, Q. virginiana, Q. laurifolia*	++	Feb–Mar
Oak, post (N), Southern	*Quercus stellata, Q. falcata*	+++	Feb–Apr
Australian pine	*Casuarina* spp.	+++	Feb–Apr/Oct–Dec
Mulberry, red, white	*Morus* spp.	++(L)	Mar–Apr

Hickory, pecan	*Carya* spp.	++(N)	Mar–Apr
Palm, sabal, date, Canary	Palmaceae	+(L)	Mar–Sep
Grasses			
Bermuda	*Cynodon dactylon*	+++	Mar–Nov
Johnson	*Sorghum halepense*	+	Apr–Aug
Bahia	*Paspalum notatum*	+	Apr–Oct
June (blue)	*Poa* spp.	+	Apr–Aug
Weeds			
Nettle group	*Urtica* spp.	++	Jan–July
Pigweed; amaranths	*Amaranthus* spp.	+	Mar–Nov
Sorrel; dock	*Rumex* spp.	+	May–Aug
Ragweed, short, giant (N)	*Ambrosia artemisiifolia, A. trifida*	++	May–Nov
Groundsel tree (shrub)	*Baccharis* spp.	+(E)	July–Sep

[a]Warmer average temperatures provide a long growing season with early appearance of common tree pollens. In certain areas, some airborne grass pollen occurs in every month; Bermuda grass is the principal source. In the south and east especially, multiple oaks contribute, including several evergreen species, e.g., willow, and laurel oaks, at lower elevations. Vast areas of yellow, long-leaf, short-leaf, and loblolly pines produce copiously, although human effects remain uncertain. Throughout the southeast the imported paper mulberry (*Broussonetia papyrifera*) has local importance.

TABLE 7.4 MAJOR SOURCES OF WINDBORNE POLLEN IN THE MIDWEST

THE MIDWEST[a]

Illinois and Indiana

Ohio and Michigan

Iowa and Missouri

Minnesota and Wisconsin

POLLEN TYPE	GENUS/SPECIES	IMPACT	PREVALENCE
Illinois and Indiana			
Trees			
Red cedar	*Juniperus virginiana*	+	Feb–Apr
Elm, American, slippery, etc.	*Ulmus americana, U. rubra, Ulmus* spp.	++	Feb–Apr
Cottonwood	*Populus deltoides*	+	Mar–Apr
Box elder	*Acer negundo*	++	Mar–Apr

Ash, white, green, etc.	*Fraxinus* spp.	++	Apr–May
Oak, red, white, bur	*Quercus rubra, Q. alba, Q. macrocarpa*	+++	Apr–May
Hickory, pecan	*Carya* spp.	++(SW)	Apr–May
Mulberry, red	*Morus rubra*	++(L)	Apr–May
Birch, river, etc.	*Betula* spp.	+	Apr–May
Walnut, black	*Juglans nigra*	+	Apr–May
Sycamore	*Platanus* spp.	+(SL)	Apr–May
Grasses			
June (blue)	*Poa* spp.	+++	Apr–July
Orchard	*Dactylis glomerata*	+++	May–July
Timothy	*Phleum pratense*	++	May–July
Red top	*Agrostis alba*	+	May–July
Bermuda	*Cynodon dactylon*	+++(S)	May–Aug
Johnson	*Sorghum halepense*	+(S)	May–Aug
Ryegrass	*Lolium* spp.	+	May–Aug
Weeds			
Ragweed, short, giant	*Ambrosia* spp.	+++	Aug–Sep

Burweed marsh elder	*Iva xanthifolia*	++(S)	Aug–Sep
Burning bush[b]	*Kochia scoparia*	++	July–Oct
Russian thistle[b]	*Salsola pestifer*	+++	July–Oct
Plantain, English	*Plantago lanceolata*	+	May–Oct
Pigweed, amaranths	*Amaranthus* spp.	+	July–Oct

Ohio and Michigan

Trees

Red cedar	*Juniperus virginiana*	+	Feb–Mar
Elm, American, etc.	*Ulmus americana, Ulmus* spp.	++	Mar–Apr
Cottonwood, aspen (N)	*Populus* spp.	+	Mar–Apr
Box elder	*Acer negundo*	+++	Apr–May
Birch, river, gray, etc.	*Betula* spp.	+	Apr–May
Ash, white, green, etc.	*Fraxinus* spp.	+++	Apr–May
Oak, red, white, bur, etc.	*Quercus* spp.	++	Apr–May
Hickory	*Carya* spp.	+	Apr–May
Sycamore	*Platanus* spp.	+(L)	Apr–May

Walnut, butternut	*Juglans* spp.	+	Apr–May
Mulberry, red	*Morus rubra*	+++(L)	Apr–May

Grasses

Orchard grass	*Dactylis glomerata*	+++	May–June
June (blue)	*Poa pratensis*	+++	May–June
Timothy	*Phleum pratense*	+++	June–July
Red top	*Agrostis alba*	+	May–June
Bermuda	*Cynodon dactylon*	+++(S)	May–July
Johnson	*Sorghum halepense*	+(S)	May–July
Ryegrass	*Lolium* spp.	+	June–July

Weeds[c]

Plantain, English	*Plantago lanceolata*	+	May–Sep
Ragweed, short, giant	*Ambrosia artemisiifolia, A. trifida*	+++	Aug–Sep
Burning Bush[b]	*Kochia scoparia*	++(L)	Aug–Sep
Pigweed; amaranths	*Amaranthus* spp.	+	Aug–Sep

Iowa and Missouri

Trees

Red cedar	*Juniperus virginiana*	+	Feb–Apr
Elm, American, slippery, etc.	*Ulmus* spp.	++	Feb–Apr
Oak, white, red, bur, etc.	*Quercus* spp.	+++	Mar–Apr
Cottonwood, eastern, swamp (SE)	*Populus deltoides, P. heterophylla*	+	Mar–Apr
Red maple	*Acer rubrum*	+(SE)	Mar–Apr
Box elder	*Acer negundo*	++(N)	Mar–Apr
Willow, black, etc.	*Salix nigra, Salix* spp.	+	Mar–Apr
Oak, white, red, bur, etc.	*Quercus* spp.	+++	Mar–May
Ash, green, white, etc.	*Fraxinus* spp.	+(S)	Apr–May
Mulberry, red	*Morus rubra*	++(L)	Apr–May
Hickory, pecan	*Carya* spp.	++	Apr–May
Sycamore, eastern	*Platanus occidentalis*	+	Apr–May
Butternut (E), black walnut	*Juglans cinerea, J. nigra*	+(L)	Apr–May

Grasses

Both Bermuda and the ryegrass-related, more northern species flower April–July (Aug).

Weeds

Strongly similar to Illinois and Indiana with the addition of rough marsh elder (S) and hemp (*Cannabis sativa*) in extreme NW Iowa as ++ factors as well as Palmer amaranth (++) in western Missouri.

Minnesota and Wisconsin

Trees

Juniper, red cedar (S)	*Juniperus* spp.	++	Apr–May
Cottonwood, aspen	*Populus* spp.	+	Apr
Maple, red, sugar, black, box elder	*Acer* spp.	++	Apr–May
Birch, yellow, paper, etc.	*Betula* spp.	++	Apr–May
Ash, white, green, etc.	*Fraxinus* spp.	++	Apr–May
Oak, red, bur, pin, white, etc.	*Quercus* spp.	+++	Apr–May
Mulberry, red	*Morus rubra* (S)	++(L)	May
Hickory	*Carya* spp.	+	May
Walnut black	*Juglans nigra* (S)	+	May

Grasses

Orchard	*Dactylis glomerata*	+++	May–June
June (blue)	*Poa pratensis*	+++	June–July
Timothy	*Phleum pratense*	+++	June–July
Red top	*Agrostis alba*	+	June–July
Ryegrass	*Lolium* spp.	++	June–Aug
Weeds			
Plantain, English	*Plantago lanceolata*	+	June–Aug
Burweed marsh elder	*Iva xanthifolia*	+++(W)	July–Sep
Russian thistle[b]	*Salsola kali*	++(W)	July–Sep
Amaranths	*Amaranthus* spp.	+	July–Sep
Hemp	*Cannabis sativa*	++(L)	July–Sep
Ragweed, short, giant	*Ambrosia artemisiifolia, A. trifida*	+++	Aug–Sep

[a]This broad, largely agricultural area forms the transition between the Great Plains and the (traditional) eastern forest domain. To the west, woodlands are increasingly confined to river bottoms. Bermuda becomes a principal grass pollen below central Ohio, Indiana, and Illinois, whereas the more northern types (i.e., orchard, timothy, june, red top, and ryegrass) predominate around, and west of, the Great Lakes. Sorrel and dock pollen is a variable but usually modest spring factor throughout. Nettle (-like) pollen is surprisingly abundant (July–August) in many areas, but sources such as wood nettle (*Laportea canadensis*) and a native parietaria (*Parietaria pennsylvanica*) may also contribute.

[b]Additional chenopod sources are negligible by comparison.

TABLE 7.5 MAJOR SOURCES OF WINDBORNE POLLEN IN THE GREAT PLAINS

THE GREAT PLAINS[a]

North and South Dakota

Kansas and Nebraska

Oklahoma and Texas

Colorado, Wyoming, and Montana

POLLEN TYPE	GENUS/SPECIES	IMPACT	PREVALENCE
North Dakota and South Dakota			
Trees			
Juniper, red cedar	*Juniperus* spp.	+	Mar–May
Cottonwood, aspen	*Populus* spp.	++	Mar–Apr
Elm, American, Siberian, etc.	*Ulmus* spp.	+++	Mar–Apr Aug–Oct
Ash, white, green, etc.	*Fraxinus* spp.	++(S)	Apr–May
Box elder	*Acer negundo*	++	Apr–May
Birch, paper, yellow, etc.	*Betula* spp.	+	Apr–May

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Ash, white, green, etc.	*Fraxinus* spp.	+	Apr–May
Oak, bur, white (E), etc.	*Quercus* spp.	+++	Apr–May
Mulberry, red	*Morus rubra*	++	May
Grasses			
June (blue)	*Poa pratensis*	+++	May–July
Timothy	*Phleum pratense*	++	June–July
Orchard (E)	*Dactylis glomerata*	+	May–July
Brome (chess)	*Bromus* spp.	+	May–July
Wheatgrass, crested, western, etc.	*Agropyron* spp.	+	June–July
Weeds			
Burning bush	*Kochia scoparia*	+++[a]	July–Sep
Russian thistle	*Salsola kali*	+++[a]	July–Sep
Western water hemp	*Acnida tamarascina*	++	July–Sep
Pigweed, amaranths	*Amaranthus* spp.	+	July–Sep
Nettle	*Urtica* spp.	+	July–Aug
Hemp	*Cannabis sativa*	++(E)	July–Aug

Ragweed, short, giant, perennial, etc.	*Ambrosia* spp.	+++	Aug–Sep

Kansas and Nebraska

Trees

Red cedar, juniper	*Juniperus* spp.	++	Feb–Apr
Elm, American	*Ulmus americana*	+++	Feb–Mar
Box elder	*Acer negundo*	+	Mar–Apr
Cottonwood	*Populus deltoides*	+	Mar–Apr
Oak, white, bur, post (E), etc.	*Quercus* spp.	++	Apr–May
Ash, green	*Fraxinus pennsylvanica*	+(E)	Apr–May
Mulberry, red	*Morus rubra*	++(SE)	Apr–May

Grasses

Strongly similar to North and South Dakota.

Weeds

Strongly similar to North and South Dakota; Palmer amaranth is a factor in eastern Kansas.

Oklahoma and Texas

Trees

Mountain cedar, red cedar, Juniper	*Juniperus ashei, J. virginiana, Juniperus* spp.	+++	Dec–Apr
Elm, American, slippery, etc.	*Ulmus* spp.	+++	Jan–Mar
Cottonwood	*Populus deltoides*	+	Mar–Apr
Ash, green, white, etc.	*Fraxinus* spp.	++	Feb–Apr
Sugarberry; hackberry	*Celtis* spp.	++	Feb–Apr
Oak, bur, post, live (SE), etc.	*Quercus* spp.	+++	Feb–May
Mulberry, red	*Morus rubra*	++	Mar–Apr
Box elder	*Acer negundo*	+	Mar–Apr
Willow, black	*Salix nigra*	++	Mar–May
Mesquite	*Populus glandulosa*	+(W)	Mar–May
Hickory, pecan	*Carya* spp.	+(L)	Apr–May
Osage orange	*Maclura pomifera*	++(E)	Apr–June
Elm, cedar	*Ulmus crassifolia*	+++	Aug–Oct
Juniper, red berry	*Juniperus pinchotii*	+++	Sep–Nov

Grasses

June (blue)	*Poa pratensis*	++	Apr–Aug
Orchard	*Dactylis glomerata*	+	May–July
Bermuda	*Cynodon dactylon*	+++	May–July
Ryegrass	*Lolium* spp.	+	June–Aug
Johnson	*Sorghum halepense*	+	May–Sep

Weeds

Burning bush[b]	*Kochia scoparia*	++	June–Sep
Russian thistle[b]	*Salsola kali*	++	June–Sep
Water hemp, western[b]	*Acnida tamariscina*	++(N)	June–Sep
Scales, saltbush[b]	*Atriplex* spp.	++(W)	June–Sep
Marsh elder, burweed (N), rough (E)	*Iva* spp.	++	Aug–Oct
Ragweed, short, giant, perennial, southern (E)	*Ambrosia* spp.	+++	Aug–Oct

Colorado, Wyoming, and Montana

Trees

Juniper, common, Utah (S), one-seeded (S), rocky mountain, etc.	*Juniperus* spp.	+++	Feb–May

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Elm	*Ulmus* spp.	++	Feb–Apr
Cottonwood, eastern (E), black (NW), fremont, narrowleaf, etc.; aspen, quaking (W)	*Populus* spp.	+	Mar–June
Willow, pacific, peach leaf, etc.	*Salix* spp.	+	Mar–May
Alder, mountain, etc.	*Alnus* spp.	+	Mar–Apr
Maple, rocky mountain, etc., box elder	*Acer* spp.	+	Apr–May
Oak, gambel's	*Quercus gambelii*	++	Apr–June
Grasses			
June (blue)	*Poa* spp.	++	June–Aug
Brome	*Bromus* spp.	+	May–July
Fescue	*Festuca* spp.	+	June–Aug
The contribution of these and other grass genera to the modest total levels recorded, including *Koeleria, Agropyron, Buchloe,* and *Bouteloua,* remains speculative.			
Weeds			
Russian thistle[c]	*Salsola kali*	+++	June–Oct
Burning bush[c]	*Kochia scoparia*	+++	June–Oct

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Scales, saltbush[c]	*Atriplex* spp.	+++	June–Oct
Sages	*Artemisia* spp.	++	July–Oct
Ragweeds[d]	*Ambrosia* spp.	++	July–Sep
Burweed marsh elder	*Iva xanthifolia*	+	July–Sep
Sorrel, dock (L)	*Rumex* spp.	+(N)	May–July

[a]This region was previously the domain of long (east) and short (west) grass prairies; however, little original cover remains, and grass pollen levels are moderate. Grass pollen sources are also numerous and difficult to assign rank. Most woodland is limited to river courses and related wetlands, except in the Northwest (Rocky Mountains), South and Central (Texas), and eastern Oklahoma.

[b]Additional chenopods and amaranths appear to make small contributions, by comparison. Moderate levels of partly wind-pollinated composites such as *Parthenium hysterophorus* occur, but health impact remains unclear.

[c]Pollen production of types listed far exceeds that of other chenopods and amaranths.

[d]Prominently including the bur ("false") ragweeds previously designated *Franseria* (now *Ambrosia*).

TABLE 7.6 MAJOR SOURCES OF AIRBORNE POLLEN IN THE SOUTHWEST

THE SOUTHWEST[a]

Arizona and New Mexico

Nevada and Utah

POLLEN TYPE	GENUS AND SPECIES	IMPACT	PREVALENCE
Arizona and New Mexico			

Trees

Mountain cedar	*Juniperus ashei*	+++(SE)	Dec–Feb
Ash, velvet, etc.	*Fraxinus* spp.	++(L)	Jan–Apr
Cypress, Arizona	*Cupressus arizonica*	+++	Feb–Apr
Juniper, cedar	*Juniperus* spp.	+++	Feb–May
Elm	*Ulmus* spp.	+++	Feb–May
Cottonwood, fremont, etc., aspen, quaking (W)	*Populus fremontii, Populus* spp.	+	Feb–May
Mulberry, white	*Morus alba*	++	Apr–June
Olive	*Olea europaea*	+++(L)	Apr–June
Box elder	*Acer negundo*	+(N, L)	Apr–May
Oak, gambel's, etc.	*Quercus gambelii, Quercus* spp.	++(L)	Apr–June
Mesquite	*Prosopis* spp.	+	Apr–June

Grasses

Bermuda	*Cynodon dactylon*	++	Apr–Sep
Johnson	*Sorghum halepense*	+(L)	Apr–Aug
June (blue)	*Poa* spp.	+(L)	Apr–July

The relative contributions of other types must still be defined.

Weeds			
Ragweed, canyon, rabbit bush, burroweed	*Ambrosia ambrosioides, A. deltoidea, A. dumosa*	+++	Mar–May
Sugar beet	*Beta vulgaris*	+(L)	Apr–June
Russian thistle[b]	*Salsola kali*	++	June–Sep
Burning bush	*Kochia scoparia*	+(N)	June–Sep
Scales, saltbush	*Atriplex* spp.	++	June–Sep
Sage	*Artemisia* spp.	++(L)	June–Sep
Ragweeds, short, slender, etc.	*Ambrosia* spp.	+	Aug–Oct

Nevada and Utah

Trees			
Elm	*Ulmus* spp.	+(L)	Feb–Mar
Juniper, cedar	*Juniperus* spp.	++	Feb–May
Box elder	*Acer negundo*	+(L)	Apr–May
Cottonwood, aspen	*Populus* spp.	+(L)	Apr–May
Ash, velvet, etc.	*Fraxinus* spp.	+++(L)	Apr–May

Mulberry	*Morus* spp.	+(L)	Apr–May
Mesquite	*Prosopis* spp.	+(L)	Apr–June

Grasses

See Arizona and New Mexico listing and note.

Weeds

Scales, saltbush	*Atriplex* spp.	+++	July–Sep
Russian thistle[c]	*Salsola pestifer*	+++	July–Sep
Ragweed, annual bur, etc.	*Ambrosia acanthicarpa, Ambrosia* spp.	+	Aug–Sep
Sage	*Artemisia* spp.	+++	Aug–Sep

[a]This group of states is best known for its flat arid terrain and mountain ranges, and fewer potent "hay fever plants." However, multipurpose irrigation is extensive, creating broad "islands" of pollen exposure with a background that is neither simple nor fully described.

[b]Contribution by related species is probably small.

[c]Additional chenopods (and amaranths), including burning bush, carelessweeds, and greasewood, are also variable contributors to exposure.

TABLE 7.7 MAJOR SOURCES OF AIRBORNE POLLEN IN THE NORTHWEST

THE PACIFIC NORTHWEST[a]

POLLEN TYPE	GENUS AND SPECIES	IMPACT	PREVALENCE

Idaho, Oregon, and Washington

Trees			
Cedar, juniper[b]	*Juniperus, Thuja,* other Cupressaceae[b]	+++	Jan–May
Alder, red, white	*Alnus rubra, rhombifolia*	+++	Feb–May
Cottonwood, black, etc., aspen	*Populus* spp.	++	Feb–Apr
Birch, paper, etc.	*Betula* spp.	+++(NW)	Feb–Apr
Willow, pacific, Sitka, etc.	*Salix* spp.	+(L)	Feb–Apr
Elm	*Ulmus* spp.	+(L)	Feb–Mar
Box elder	*Acer negundo*	+++	Mar–Apr
Ash, Oregon, etc.	*Fraxinus* spp.	+	Mar–Apr
Oak, Oregon white, California black, etc.	*Quercus garryana, Q. kelloggii, Quercus spp.*	+(L)	Apr–May
Walnut, English, etc.	*Juglans regia, Juglans* spp.	++(L)	Apr–May
Grasses			
June (blue)	*Poa pratensis, Poa* spp.	+++	May–Aug
Brome	*Bromus* spp.	+(E)	May–Sep
Timothy	*Phleum pratense*	+	June–Aug

Ryegrass, perennial, etc.	*Lolium* spp.	+(L)	June–Aug
Red top	*Agrostis alba*	+(L)	June–Sep
Weeds			
Nettle and related types	Urticaceae[c]	+	May–July
Sorrel, dock	*Rumex* spp.	+	May–July
Russian thistle	*Salsola kali*	++(E)	July–Sep
Pigweed, amaranths	*Amaranthus* spp.	+	July–Sep
Sage	*Artemisia* spp.	+++(EL)	July–Sep
Additional chenopods appear to contribute little, by comparison.			

[a]The north–south course of the Cascades Mountain Range is the arbiter of moisture here, with well-watered western slopes, a dryer region downwind, and, ultimately, high desert to the east. Regional features include red alder as a preeminent tree pollen source, a grass flora recalling the Northeast and heightened grass pollen levels in the Willamette valley of Oregon, where seed is produced commercially. Idaho presents a mountainous spine with a patchwork of dry and moist, agricultural lowlands.

[b]May include other sources, among them incense cedar (*Calocedrus decurrens*) and Port Orford cedar (*Chamaecyparis lawsoniana*); hence, the family is listed.

[c]Contributions of types other than nettle (*Urtica* spp.) are uncertain; hence the family name is used here.

TABLE 7.8 MAJOR SOURCES OF AIRBORNE POLLEN IN CALIFORNIA

CALIFORNIA[a]

GENUS AND SPECIES			
Trees			
Alder, red, white, etc.	*Alnus rubra, A. rhombifolia, Alnus* spp.	+(W)	Jan–Feb
Cypress; cedar; juniper	*Cupressus* spp., *Juniperus* spp.	++	Jan–Apr
Oak, black, interior live, coast live (W), etc.	*Quercus kelloggii, Q. wislizenii, Q. agrifolia, Quercus* spp.	+++	Jan–May
Ash, velvet (S) Oregon, etc.	*Fraxinus velutina, F. latifolia, Fraxinus* spp.	++	Jan–Apr
Cottonwood, Fremont	*Populus fremontii*	++	Feb–Apr
Acacia (S)	*Acacia* spp.	+(L)	Feb–Oct
Sycamore, California	*Platanus racemosa*	+	Feb–Apr
Mulberry, white, etc.	*Morus alba, Morus* spp.	+++	Mar–May
Australian pine (Casuarina)	*Casuarina* spp.	+	Mar–May
Walnut, English, etc.	*Juglans regia, Juglans* spp.	+	Mar-Apr
Olive (S)	*Olea europaea*	+++(L)	Apr–June
Castor bean[b]	*Ricinus communis*	+(L)	Apr–July
Elm, Siberian, etc.	*Ulmus pumila, Ulmus* spp.	+++(L)	Aug–Oct

Grasses			
Bermuda	*Cynodon dactylon*	+++	Apr–Oct
Rye	*Lolium* spp.	+(N)	May–Aug
Brome	*Bromus* spp.	+	Apr–Sep
Fescue	*Festuca* spp.	+	May–Sep
Johnson	*Sorghum halepense*	+(S)	May–Sep
June (blue)	*Poa* spp.	+	Apr–Sep

Diverse additional species are noted and may contribute.

Weeds			
Sage	*Artemisia* spp.	+++(S)	June–Oct
Russian thistle[c]	*Salsola kali*	+++(L)	June–Sep
Scale, saltbush[c]	*Atriplex* spp.	++(E)	June–Sep
Ragweed (L)	*Ambrosia* spp.	++(E, L)	July–Sep
Pigweed, amaranth	*Amaranthus* spp.	+	July–Sep
Nettle	Urticaceae	+(L)	Apr–Sep
Burning bush[c]	*Kochia scoparia*	++(S)	Mar–July

as care in discriminating the many circumscribed pollen sources. A complex oak flora is prominent, and (northern) conifer pollens of uncertain significance abound. Bermuda is the dominant grass offender, with many more minor sources recognized. To the south, seasonal rains determine pollen output, both varying between extremes. Clinical reactivity to eucalyptus, bottle brush, maples, and mesquite probably is uncommon, although skin test reactivity is documented.

[b]Additional shrubby species, including pepper-tree (*Schinus* spp.), chamise (*Adenostoma*), and blue blossom or California lilac (*Ceanothus* spp.), produce appreciable windborne pollen of uncertain significance clinically.

[c]Pollen output by other chenopods is comparatively minor.

TABLE 7.9 MAJOR SOURCES OF AIRBORNE POLLEN IN ALASKA AND HAWAII

THE NONCONTIGUOUS UNITED STATES

Alaska

Alaska has a somewhat limited wind-pollinated flora and a short growing season. Throughout the state, birch (*Betula papyrifera*) pollen is paramount, and climate change has had an impact, with birch pollen concentrations showing significant increase in recent years. Grasses and sedges are secondary sources, with Sitka spruce (*Picea sitchensis*) and mountain alders (*A. sinuata and A. tenuifolia*) locally significant. Quaking aspen, balsam poplar, and black cottonwood are factors in moist areas, where brief pollination by several scrubby willows also is recognized. Primarily in the south, limited pollen shedding by docks, chenopods, amaranths, ragweeds, and sages is recognized.

Hawaii

With its unfailing pleasant temperatures and high humidity, Hawaii provides perennially favorable conditions for much plant growth. However, like many other tropical sites, abundant, wind-pollinated species are limited. Bermuda grass pollen is present potentially at all times, but other sources such as sugar cane (*Saccharum officinarum*), Johnson grass (*Sorghum halepense*), panic grasses (*Panicum* spp.), and *Pennisetum* appear minimal. Various types of weed pollen, including ragweed, occur but are not abundant. When grouped, mesquite (*Prosopis* spp.), casuarina (*Casuarina* spp.), and several palms (Arecaceae) have been implicated as occasional offenders.

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Principles of Evaluation and Treatment

Diagnosis of Immediate Hypersensitivity

MAHBOOBEH MAHDAVINIA, SHERLYANA SURJA, AND ANJU T. PETERS

Immediate hypersensitivity or *type I hypersensitivity* is defined as the presence of immunoglobulin E (IgE) antibodies in response to an allergen. This type of hypersensitivity is the underlying mechanism of multiple allergic diseases, including food allergy, allergic conjunctivitis, allergic rhinitis, atopic (allergic) asthma, immediate IgE-mediated drug hypersensitivity, and some cases of atopic dermatitis. Immediate hypersensitivity in the setting of exposure to the culprit antigen could manifest as anaphylaxis, urticaria, angioedema, and gastrointestinal and respiratory symptoms such as wheezing and/or stridor. It is noteworthy that these symptoms or conditions might have other causative explanations. Consequently, when a patient has been troubled enough by one of these symptoms to consult a physician, it is necessary to perform a complete evaluation. The first and most important step in evaluation of patients with possible immediate hypersensitivity is a detailed history to determine whether symptoms could be allergic in origin or if they have another cause. If the history is suggestive of an allergic reaction, a more specific diagnostic evaluation must

be completed in order to identify the allergen responsible for producing symptoms. The degree of sensitivity to an allergen may vary among patients, as may the degree of exposure to a particular allergen. Many patients are sensitized to multiple allergens, and the cumulative effects of exposure to several antigens may produce severe or persistent symptoms. Furthermore, the influence of nonimmunologic phenomena needs to be evaluated. Infections, inhaled irritants, fatigue, malignancies, patient perception, anxiety and so on can be important factors influencing the symptoms.

■ PATIENT EVALUATION AND HISTORY

The history provides most of the information necessary for diagnosis of any allergic condition. Diagnostic testing can help, once a detailed history is suggestive of the allergic nature of the condition, and may be indicated to confirm or refute the suspected diagnosis. It is the clinician's responsibility to select allergens appropriately and to be cognizant of potential adverse effects, particularly in patients suspected to be highly sensitized. In case of aeroallergen sensitivity, specific questions need to be asked, which can help to distinguish certain allergens. Here we have detailed specific questions or items in each section of the history and physical examination (H&P) that need to be covered to perform a thorough and adequate evaluation of an allergic condition.

History of Present Illness

The history of present illnesses (HPI) in regard to the possible allergic chief complaint needs to cover four main domains. These are: (1) the nature of the symptoms with particular attention focused on which organs are affected; (2) the timing of symptoms in association with a possible culprit; (3) if and how the symptoms were treated and whether they responded to medications; (4) whether the patient was exposed to the culprit allergens consequently; and what the symptoms were. In addition, the presence or absence of symptoms of nonallergic comorbid conditions must be determined. Here we have discussed further details about these four domains:

1. A thorough history of the chief complaints and the associated symptoms can help narrow the differential diagnosis. For example, in the case of patients complaining of upper or lower airway disease, the presence of symptoms related to the respiratory system needs to be evaluated. These symptoms include sneezing, rhinorrhea, nasal congestion, anosmia, ear fullness, palatal pruritus, ocular irritation, intermittent hearing loss, wheezing, chest tightness, dyspnea, or cough. Several allergic symptoms frequently exist simultaneously

even if the patient does not associate them with a common cause. If several of these symptoms are present, it is more likely that they all have an allergic origin. Conversely, a symptom in a single organ system, such as isolated nasal obstruction, is less likely to be allergic. Another important factor that needs to be determined in patients with respiratory symptoms is whether the symptoms are bilateral. Unilateral symptoms, whether they are ocular, nasal, or pulmonary, usually suggest the presence of nonallergic conditions, often anatomic in nature. The evaluation should address the severity of the symptoms. Symptom severity is an important information that helps decision making regarding treatment and evaluations. It can affect the extent of the diagnostic evaluation and the intensity of therapy. Whether the symptoms are nasal, ocular, pulmonary, or dermatologic, it is necessary to assess the subjective degree of discomfort they cause. Health-care providers must also take into account the patient's perceptions and expectations. Perceived severity may relate closely to its effect on spouses or parents, for example. The assessment of severity also includes more objective measures, such as frequency—the number of days that symptoms occur, number of hours that they persist, number of days lost from or being unproductive at work or school, and the number of days hospitalized. Certainly, special consideration should be given to life-threatening events such as intubations and episodes of unconsciousness or near loss of consciousness.

2. The timing of reactions in association with a possible culprit is of utmost importance. Most IgE-mediated reactions, including anaphylactic reactions, occur within minutes to hours of exposure to the allergen. For example, IgE-mediated reactions to oral antigens (i.e., food, medication) typically occur within a few minutes to 2 hours of exposure to the culprit antigen. Patients, who experience acute urticaria or potentially anaphylaxis up to 6 hours after eating beef, pork, or lamb, are the exceptions and have been sensitized to ticks, with development of anti-galactose-α-1,3-glactose ("alpha gal") IgE (1).

3. Another important part of HPI is the patient's response to previous treatment. A good response to H_1 antihistamines increases the likelihood that the symptoms have an allergic origin. Response to a bronchodilator or anti-inflammatory therapy, given either systemically or by inhalation, may give valuable information regarding the presence of reversible airway obstruction. Proper response to previously administered immunotherapy would strongly implicate an allergic problem. A rapid response to an epinephrine injection in case of acute systemic symptoms like combination of angioedema, vomiting, and shortness of breath is indicative of anaphylaxis.

4. Response to repeat exposure to suspected allergens is very important in figuring out if the initial reaction was allergic. This is especially important for food and drug allergies. If the individual has taken the food or drug allergen after the initial symptoms presented, and has tolerated it with no reaction, most probably that certain food or drug was not the cause of the symptoms, or the patient has now developed tolerance and further investigation might not be necessary.

A careful historian can often narrow the list of allergens suspected to be responsible for the symptoms of allergic diseases. This facilitates selection of further diagnostic tests and minimizes the number of tests performed. Specifically, a detailed survey of the patient's home, work, or school environment may identify potential triggers of a respiratory symptom. A history is especially important in selecting appropriate food extracts for testing because of the low specificity of *in vivo-* and *in vitro*-specific IgE testing (2).

Past Medical History

A complete medical history, including other allergic and nonallergic conditions, is necessary. For example, a history of eczema is associated with a higher likelihood of other allergic diseases such as allergic rhinitis and food allergy. Furthermore, a careful history of other conditions that can affect the diagnosis or management of immediate hypersensitive needs to be obtained.

Medication History

A complete list of medications, both prescription and over-the-counter, should be elicited and their potential role as a causative factor for the symptoms needs to be considered. For example, oral contraceptives, oral antipsychotics, certain antihypertensives, and phosphodiesterase type 5 inhibitors can cause rhinitis (3). Most cardioselective beta blockers are safe in asthmatics, but β-adrenergic blockers are rarely responsible for wheezing and dyspnea (4–6). Aspirin or nonsteroidal antagonists may worsen upper or lower respiratory symptoms in patients with aspirin-exacerbated respiratory disease—triad of chronic rhinosinusitis with nasal polyps, asthma, and aspirin sensitivity (7). Angiotensin-converting enzyme (ACE) inhibitors can produce a severe persistent cough or angioedema (8,9). Chronic use of topical decongestants in the nose or eyes may lead, respectively, to chronic nasal congestion or ocular irritation (10,11). Awareness of these reactions can prevent unnecessary and expensive allergic evaluations.

Review of Systems

The physician should establish whether there are other symptoms, in addition to the presenting complaint, that may be related to the patient's allergic condition. These questions are mostly investigated in the HPI section of the history. However, if it was not covered, it is important to inquire about lower respiratory symptoms in any patient with rhinitis. Furthermore, this information can shed light onto other comorbid conditions that a patient would not think are relevant. Asking about upper gastrointestinal symptoms in patients with asthma will help you diagnose gastroesophageal reflux disease, which can significantly affect asthma control. Similarly, eosinophilic esophagitis (EoE) is often associated with allergic rhinitis and getting a history of dysphagia or odynophagia while evaluating patients for rhinitis may potentially uncover a diagnosis of EoE.

Family History

Most allergic patients have a positive family history (12,13). Specifically ask about allergic diseases in their parents, grandparents, siblings, aunts, uncles, cousins, and children.

PHYSICAL EXAMINATION

A complete physical examination is an essential part of the evaluation for allergic conditions. Particular attention must be directed to sites affected by common allergic diseases: eyes, nose, oropharynx, ears, chest, abdomen, and skin. Here we have summarized the important examinations and findings that are associated with specific allergic conditions: conjunctivitis, rhinitis, asthma, atopic dermatitis, food allergy, and drug allergy.

Conjunctivitis

Physical findings of allergic conjunctivitis are hyperemia and edema of the conjunctiva. Occasionally, a pronounced chemosis occurs associated with a clear, watery discharge. Periorbital edema may be present, and, rarely, a bluish discoloration or an "allergic shiner" around the eyes may occur.

Rhinitis

The skin of the nose, and particularly of the upper lip, may show irritation and excoriation produced by the nasal discharge and continuous nose wiping. The examination of the nasal cavity with an anterior rhinoscope requires good exposure and adequate light. In a patient with allergic rhinitis, the inferior

turbinates usually appear to be swollen and may touch the nasal septum. They may have a uniform bluish or pearly gray discoloration, the so-called pale mucosa, but more frequently there may be adjacent areas where the membrane is red, giving a mottled appearance. One should look for nasal polyps in the nose, which would be indicative of coexisting chronic rhinosinusitis with polyps. In patients with nasal allergic disease, the ears should be examined for evidence of acute or chronic otitis media, either serous or infectious in nature. Nasal secretions also may be observed draining into the posterior pharynx, therefore, careful examination of the retropharyngeal space is an essential part of examinations in patients with rhinitis. "Cobblestoning" of retropharyngeal lymphoid tissue may be observed in the setting of chronic inflammation of the nose.

Asthma

Physical findings in asthmatic patients are highly variable, not only between patients but also in the same patient at different times. When the asthmatic patient is not having an acute exacerbation, there may be no demonstrable abnormalities on auscultation even when evidence of reversible airway obstruction can be demonstrated with pulmonary function studies. In many instances, wheezes may be heard even when the patient is feeling well. In some cases, wheezes will not be heard during normal respiration but can be heard if the patient exhales forcefully. During an acute attack of asthma, the patient is often tachycardic and tachypneic. The patient appears to be in respiratory distress and may use the accessory muscles of respiration. Mechanically, these muscles are more effective if the patient stands or sits and leans slightly forward. Intercostal, subcostal, and supraclavicular retraction, as well as flaring of the alae nasi, may be present with inspiratory effort. On auscultation, musical wheezes may be heard during both inspiration and expiration, and the expiratory phase of respiration may be prolonged. These auscultory findings tend to be present uniformly throughout the lungs in uncomplicated asthma exacerbation. Asymmetry of auscultory findings might be caused by concomitant disease such as pneumonia, or by a complication of the asthma itself, such as occlusion of a large bronchus with a mucous plug. In severely ill patients, extreme bronchial plugging and loss of effective mechanical ventilation may be associated with disappearance of the wheezing and a decrease in audible breath sounds. In critically ill patients, once alveolar ventilation has decreased significantly, they may have distant or absent breath sounds along with hypoxemia and cyanosis.

Atopic Dermatitis

The findings on physical examination of a patient with atopic dermatitis vary widely. A complete skin evaluation is necessary. The distribution of the lesions varies with the age of the patient. In an infant 4 to 6 months of age, the skin lesions commonly occur on the cheeks, scalp, ears, and the neck. Older children typically have lesions in flexural areas, specifically the antecubital and popliteal fossae. Adults may have localized involvement, such as on the hands, or generalized disease. Individual skin lesions feature initial erythema followed by a fine papular eruption. The papules may coalesce to form ill-defined plaques, or they may progress to papulovesicles that may rupture to produce oozing and crusting. These lesions uniformly are markedly pruritic. Secondary bacterial infection is frequently present and needs to be assessed. Chronic lesions are characterized by lichenification. The skin appears thickened, coarse, and xerotic. There may be moderate scaling and alteration in pigmentation. Further details are described in Chapter 15.

Urticaria and Angioedema

Urticaria is suggested by erythematous raised lesions (papules or plaques) that blanch under pressure and resolve typically within hours without sequelae, such as bruising or discoloration. Angioedema involves subcutaneous swelling most commonly of the lips, eyelids, tongue, or genitals. However, angioedema can occur in any part of the body, including the gastrointestinal tract, causing severe abdominal cramps. IgE-mediated angioedema typically resolves in 24 to 48 hours without sequelae. Angioedema that is bradykinin-mediated may require 3 to 5 days to resolve.

Anaphylaxis

During an anaphylactic episode, vital signs need to be closely monitored. Tachycardia and tachypnea are often present. Most episodes of anaphylaxis are accompanied by skin manifestations varying from flushing to urticaria and/or angioedema (14).

Upper or lower airway involvement may be present during an anaphylactic episode with tongue/laryngeal edema, stridor, or wheezing. Severe laryngeal edema or bronchospasm may result in respiratory arrest. Cardiovascular collapse owing to severe vasodilation can manifest as hypotension or cardiac arrest without skin manifestations. After successful resuscitation, hives may appear and lead to the diagnosis of anaphylaxis.

FURTHER EVALUATIONS

Before moving to diagnostic evaluation of IgE-mediated hypersensitivity reactions, it is important to know what kind of antigens (allergens) can cause this type of hypersensitivity and result in allergic conditions.

CHARACTERISTICS OF ALLERGENS

Some general characteristics of the antigens responsible for allergic diseases must be appreciated by physicians treating those allergic conditions.

The allergens most important in asthma, rhinitis, and conjunctivitis, and some cases of atopic dermatitis, are airborne inhalant allergens. Several different groups of these aeroallergens are of major clinical significance, including pollens, molds, house dust mites, cockroach, and animal dander. See Table 8.1 for a review of the important aeroallergens. Although foods may be contributing factors in cases of infantile severe eczema, acute urticaria/angioedema, or anaphylaxis, they are rarely responsible for triggering chronic respiratory symptoms and do not cause chronic urticaria/angioedema. The exception is in patients with concomitant food allergy and asthma, who can exhibit acute respiratory symptoms upon exposure to the offending food antigen. However, asthmatics without a clear history of an acute reaction after ingestion of a particular food are not likely to have food allergy. The main features and characteristics of airborne inhalant allergens are detailed here.

Outdoor Allergens

Pollen

Plant pollens are among the most important antigens that cause clinical respiratory symptoms. Most plant pollens are rich in protein and therefore potentially antigenic. Whether specific pollen causes symptoms depends on several factors. The pollens that routinely cause illness usually fulfill four criteria: (1) the pollen grains are produced in large quantities by a plant that is prevalent locally; (2) they depend primarily on the wind for dispersal; (3) they are small, 2 to 60 μm in diameter; and (4) they can induce an immunologic response.

Many plants produce pollen grains that are large, thick, and waxy. The transfer of these pollens between flowering plants is accomplished by insects. These pollens are not widely dispersed in the air and therefore rarely clinically significant. In contrast, pollen grains that are small and light could be dispersed by the wind and cause significant allergic symptoms if they are antigenic. In the United States, many trees, grasses, and weeds produce large quantities of highly

antigenic, windborne pollen. The seasonal occurrence of tree, grass, and weed pollens varies with the geographic location, as discussed in Chapter 7. Even though many factors may alter the total amount of pollen produced in any year, the season for pollination of a plant remains remarkably constant year to year in an area. This is because pollen release is determined by length of day, which is consistent from year to year. The treating physician must know which pollens abound in the patient's primary geographic area and the seasons for pollination.

TABLE 8.1 SYMPTOMS CHARACTERISTICALLY PRODUCED BY COMMON AEROALLERGENS

ANTIGENS	SYMPTOMS
Pollens	Seasonal symptoms or seasonal exacerbation of symptoms
Mold spores	Perennial symptoms in warm climates
	Seasonal exacerbations in some moderate climates
	Reduced symptoms when living or vacationing in dry climates
	Symptoms that decrease with snow
	Sudden increase in symptoms if exposed to basements, moldy hay or leaves, barns or silos, dairies, breweries, food storage areas, buildings with contaminated air conditioning systems, rotting wood, or any location that might have high humidity
	Rarely may have exacerbation after ingesting mold products
House dust mite	Characteristically perennial symptoms
	Exacerbations when making beds, cleaning, or dusting the home
	Occasional exacerbations when entering older homes with older furnishings
Animal danders	Perennial symptoms
	Marked improvement in symptoms when leaving home for several days or weeks, if animal lives in the home
	Sudden exacerbations of symptoms after a new pet has been introduced into the home
	Sudden increase in symptoms when visiting a home where animals live
	Less frequently, sudden increase in symptoms when playing with an

Fungi and Molds

Thousands of different fungi exist. The role of molds in many conditions is speculative, but some species (such as *Alternaria alternata*) have been implicated in exacerbating symptoms in mold-allergic individuals (15,16). Because fungi can colonize almost every possible habitat and reproduce spores prolifically, the air is seldom free of their spores. Consequently, fungi can play a major role in some patients with perennial symptoms. However, seasonal or local influences can greatly alter the number of airborne spores.

Periods of warm weather with relatively high humidity allow optimal growth of molds. If this period is followed by hot, dry, windy weather, the spores often become airborne in large concentrations. "Thunderstorm asthma" has been associated with increases in mold spores, weeds, and grass pollen (15,17,18). A frost may produce a large amount of dying vegetation, but the decreased temperature may reduce the growth rate of fungi. In contrast, summer and fall provide the relative warmth, humidity, and adequate substrate necessary for the growth of fungi.

High local concentrations of mold spores are encountered frequently. Deep shade may produce high humidity because of water condensing on cool surfaces. High humidity may occur in areas of water seepage, such as basements, refrigerator drip trays, or garbage pails. Food storage areas, dairies, breweries, air conditioning systems, piles of fallen leaves or rotting wood, and barns or silos containing hay or other grains may provide nutrients as well as a high humidity, and therefore may have high concentrations of mold spores.

Indoor Allergens

The indoor environment contains multiple potential allergens including fungi, dust mites, pet dander as well as cockroaches and mouse allergens (19–22).

Dermatophagoides species are recognized as the major source of antigens in house dust (23). House dust mites are by far the most predominant allergen sources in many regions, especially those with tropical climates where populations are perennially exposed mainly to storage mites such as *Lepidoglyphus destructor, Tyrophagus putrescentiae, Aleuroglyphus ovatus*, and

Blomia tropicalis (24–26).

Carpeting, bedding, upholstered furniture, and draperies are the main sanctuaries of dust mites in a home. They are discussed in detail in Chapter 10.

Dust mite–sensitive patients may have perennial symptoms, although these may be somewhat improved outdoors with less humidity or during the summer months. They may have a history of sneezing, lacrimation, rhinorrhea, or mild asthma whenever the house is cleaned or the beds are made. In many dust mite–sensitive patients, the history is not so obvious, and the presence of perennial symptoms is the only suggestive feature.

Cockroach is an important allergen in urban areas. Exposure and IgE sensitivity to cockroach is associated with increased asthma morbidity especially in urban children (27,28). Both dust mite and cockroach allergens become airborne in rooms with activity. In the absence of activity, airborne levels decline rapidly. Several studies have found a strong correlation of a high level of mouse allergen exposure with poor asthma outcomes in urban asthmatic children (22,29,30).

Certain occupational groups such as laboratory workers, veterinarians, ranchers, farmers, magicians, or pet-shop owners may be exposed to an unusual variety of animal dander (31–35).

Patients with clinical sensitivity to household pets or laboratory animals may have history similar to that of dust mite–sensitive patients with perennial symptoms. In addition, they may have symptomatic improvement when leaving the home or work environment. Symptoms may persist outside the exposure area because allergens are often carried on clothing. If a physician does not inquire about the presence of a pet, a patient's symptoms may be completely misinterpreted and improper therapy may be prescribed.

Food and Drug Allergens

IgE-mediated food reactions may be responsible for anaphylaxis or urticarial reactions. These are discussed further in Chapter 14. Similarly, certain drugs or venom stings may be responsible for immediate hypersensitivity reactions, which are discussed in Chapters 17 and 12, respectively.

Nonimmunologic contributing factors frequently aggravate allergic conditions and should always be evaluated. Primary irritants such as tobacco smoke, pollutants, paint fumes, hair spray, perfumes, cleaning agents, other strong odors, or more generalized air pollution may precipitate flares of allergic respiratory

conditions (36,37). In addition, infections (especially viral), weather changes, exercise, and stress can worsen airway allergic diseases (38).

■ EVALUATIONS OF IGE-MEDIATED SENSITIVITY

Skin Tests

Skin prick tests are the corroborative diagnostic tests of choice for many allergic diseases. Skin tests are routinely used in the evaluation of conjunctivitis, rhinitis, asthma, and anaphylaxis. A positive skin test result demonstrates only the presence of a specific IgE antibody or of sensitization. A positive result does not necessarily indicate that a person has a current allergic disease. Said differently, sensitization may not correspond with a clinically significant reaction to a specific antigen.

Population studies have demonstrated that asymptomatic individuals may have positive skin tests (39–42), but a subgroup of symptomatic rhinitis individuals may present with negative skin test results and positive nasal provocation tests, which may indicate local allergic rhinitis (43,44). The clinical history should guide the selection of aeroallergens for which skin tests are performed. Geographic location and antigen cross-reactivity should also be considered. Satisfactory information can usually be obtained with a relatively small number of tests that are carefully chosen.

Pathophysiology of Skin Testing

Immediate responses elicited by skin testing peaks in 15 to 20 minutes and involves production of the wheal and flare reaction characteristic of atopic sensitization. Mast cell degranulation and subsequent release of histamine and other mediators is responsible for the immediate reaction (45). The wheal and erythema reaction can be reproduced by introduction of histamine into the skin.

Skin Testing Techniques

Currently, two methods of skin testing are widely used: prick or epicutaneous tests and intradermal tests. Both are easy to perform, fairly reproducible, reliable, and relatively safe. The tests should be read in 15 to 20 minutes at which time both wheal and erythema (flare) should be reported in millimeters.

Skin prick tests are more specific than intradermal tests in corroborating allergic disease (46,47). These tests can be performed with a minimum of equipment and are the most convenient and precise method of eliciting the presence of IgE antibodies. A plastic tipped device can be utilized with

penetration from a 90 degree perspective. Alternatively, a drop of allergen extract is placed on the skin surface and a sharp instrument (hypodermic needle, solid bore needle, blood lancet) is gently advanced so as to penetrate into the epidermis through the drop at a 45 to 60 degree angle to the skin (48). The epidermis is then gently raised without causing any bleeding. If appropriate antigen concentrations are used, there is relatively little risk of anaphylaxis, although large local skin reactions may occur occasionally (49).

If the skin-prick test result is negative, an intradermal test may be performed by injecting the allergen into the dermis. The skin is held tense and the needle is inserted almost parallel (tangential) to its surface, just far enough to cover the beveled portion. Allergen extract (0.02 to 0.05 mL) (48) is injected using a 26-gauge needle to form a small bleb. There is a very small risk of a systemic reaction with intradermal testing. Therefore, dilute concentrations of the antigen are used. If the skin-prick test is positive, the intradermal test is not needed and should be avoided. Intradermal tests are more sensitive but less specific compared to prick/puncture tests. Some studies have questioned the clinical utility of intradermal testing if prick tests are negative (46,50–53). Intradermal testing of food allergens is avoided due to the high false-positive rate and the risk of systemic reactions (54).

Reading and Grading of Skin Tests

Currently no standardized system exists for recording and interpreting skin test results. Many systems for grading positive reactions have been devised. A simple semi-quantitative system that measures wheal and erythema is shown in Table 8.2 but is no longer used by many clinicians because of high inter-physician variability (55). In general, a wheal size of 3 mm or greater than the negative control suggests the presence of allergen specific IgE antibody (48). The size of the reaction may be recorded as a mean wheal diameter, $(D + d)/2$ (with D indicating the largest diameter of the wheal and d indicating the largest diameter orthogonal to D) (48). One study has shown that the longest wheal diameter alone, as opposed to the mean diameter, seems to be a better surrogate marker of the wheal surface, and has been proposed as the optimal method for evaluating skin test results (56).

TABLE 8.2 GRADING SYSTEM FOR SKIN TESTING

GRADE	SKIN APPEARANCE
0	No reaction or a reaction no different than negative control

1+	Erythema <21 mm and larger than negative control No wheal formation
2+	Erythema >21 mm and larger than negative control Wheal formation of <3 mm
3+	Erythema and wheal formation of ≥3 mm without pseudopod
4+	Erythema and wheal formation of ≥3 mm with pseudopod formation

Adapted from Doan T, Zeiss CR. Skin testing in allergy. *Allergy Proc*. 1993;14:110–111, with permission.

These tests rely on the skills of the tester. Both positive and negative controls must be performed for the proper interpretation of the test results. Histamine is the preferred positive control. Saline, 50% glycerinated HSA saline (48), or extract diluent may be used for the negative control. Because large reactions at adjacent test sites might coalesce, the test sites should be at least 2 cm apart (57). In cases of dermatographism, there may be reactivity at the control site. This should be noted when the results of the tests are recorded. Interpretation of the tests is then more difficult and should be performed with caution. Tests that do not clearly have a greater reaction (of at least 3 mm) than the negative control should be considered indeterminate. Reliability of prick and intradermal tests could be affected by the personnel's skills, test instruments, color of the skin, and potency of the extract. Both false-positive and false-negative skin test results may occur because of improper technique. False-positive results may also result from dermatographism or from "irritant" reactions. For intradermal skin tests, injection of an excessive volume (>0.05 mL) can cause mechanical irritation of the skin, resulting in false-positive results. False-negative skin tests may be caused by outdated or poorly reactive extracts or decreased skin reactivity owing to disease or older age.

Interpretation of Skin Test Results

Table 8.3 provides a guide for the interpretation of skin tests to aeroallergens. Positive skin tests with a corresponding history of clinical reactivity may strongly incriminate an antigen. Conversely, negative skin tests (to

aeroallergens) with a negative history exclude the antigens as being clinically significant. Interpretation of skin tests that do not correlate with the clinical history or physical findings is less straightforward. If there is no history suggesting sensitivity to an aeroallergen, and the skin test result is positive, the patient can be interviewed and examined during a period of maximal exposure to the antigen (i.e., peak pollen season). At that time, if there are no symptoms or physical findings of allergic disease, the positive skin test finding may be ignored based on the lack of clinical relevance. Positive results may also precede the onset of clinical symptoms (40,41). A study of college students (41) demonstrated that asymptomatic students who were positive for skin test were more than twice as likely to develop allergic rhinitis 23 years later than asymptomatic students who were negative for skin test. Having a positive skin test was found to be a significant risk factor for developing asthma as well.

Interpretation of Skin Testing for Food Allergens

In general, properly performed skin prick tests to food allergens have a high negative predictive value (58,59), with much lower positive predictive values at 30% to 65% (58–63). Therefore, a positive test indicates sensitization that may or may not be symptomatic. As with aeroallergens, a response of a 3 mm wheal or greater (associated with a flare) to food allergens indicates the presence of specific IgE in the setting of a negative saline response. Larger wheal sizes (>8 to 10 mm) indicate an even greater likelihood of clinical reactivity with ingestion (62). Intradermal testing is contraindicated for food allergens because of its high false-positive rate and risk of systemic reactions (anaphylaxis). Occasionally, patients with a history highly suggestive for food allergy may have negative skin test results for the suspected antigens. In these cases, the H&P should be revisited, and the possibility of false-negative skin test results must be excluded. Specific IgE to foods may be checked in the serum to confirm lack of food allergy, and if present then the presence of food allergy in the setting of a clinically relevant history. Oral food challenges are still the method of choice to confirm food allergies. Studies have determined specific values for certain foods that obviate the need to confirm clinical sensitivity by challenge test (64).

TABLE 8.3 INTERPRETATION OF SKIN TESTS

IF	AND	THEN
History suggests sensitivity,	skin tests are positive,	strong possibility that antigen is responsible

History does not suggest sensitivity,	skin test results are positive,	may want to observe patient during time of high natural exposure
History suggests sensitivity,	skin tests are negative,	1. Review medications the patient has taken: antihistamines and antidepressants
		2. Review other reasons for false-negative tests such as poor quality of testing materials or poor technique or assess for other conditions that cause similar symptoms
		3. Observe patient during a period of high natural exposure
		4. Perform provocative challenge (rarely)

Skin testing for Hymenoptera venoms, latex allergy, and drug hypersensitivity is discussed in Chapters 12 and 17.

Extracts for Skin Tests

Skin testing should be performed with clinically relevant, potent, and stable allergens. Currently, a number of standardized allergenic extracts are available and should be used when possible. Standardized extracts increase skin test reproducibility, decrease false positives, and facilitate cross-comparisons among extracts from different physicians (65). Factors that decrease stability of extracts include extended periods of storage, temperatures above 40°F or below 33°F, and the presence of proteases. Refrigeration of extracts and addition of glycerin diminishes loss of potency (66). Food extracts often lose potency over time and may be less stable, and therefore a skin test with freshly made extract is preferable. Prick testing with fresh plant food may be advisable if a food extract skin test is negative and there is suspicion for food allergy. Currently, many recombinant allergen extracts are being investigated for skin testing (67,68). Even though, the use of these recombinant allergens may be useful to improve

allergy diagnosis and allergy treatment by means of immunotherapy, these tools are still not available for routine clinical applications (69,70).

Late Phase Response

Occasionally delayed reactions characterized by erythema and induration will occur at the site of skin tests. They become apparent 1 to 2 hours after application, peak at 6 to 12 hours, and usually disappear after 24 to 48 hours (71). In contrast to the immediate reactions, they are inhibited by conventional doses of corticosteroids but not by antihistamines (72–74). It is uncertain if the presence of a cutaneous late phase response (LPR) to an antigen will predict occurrence of LPR in the nose or lung of the same patient. Some investigators believe there is a correlation and others do not (75–80).

Adverse Reactions from Skin Testing

Large local reactions at the site of testing are the most common adverse reactions from skin testing. These usually resolve with cold compresses and antihistamines. Systemic reactions are rare but have been reported, particularly with intradermal testing. They usually occur within 30 minutes of testing (81–83). In a recent survey of American College of Allergy, Asthma, and Immunology and American Academy of Allergy, Asthma, and Immunology members, 74 out of 269 practices reported at least one systemic reaction to skin testing between 2008 and 2012, an average of one mild to moderate systemic reaction per each center in a 4-year period. Most of the reported reactions (54%) were with intradermal skin testing (49). The rate of systemic reactions after skin test was reported by another recent study to be 0.077%. Systemic reactions were associated with a history of severe reactions to the culprit allergen (84). Patients with unstable asthma are at a greater risk of an adverse reaction from skin testing and should not be tested until their asthma is stabilized. Other risk factors for systemic reactions include intradermal testing (as opposed to skin prick test) and atopic dermatitis (85,86).

Emergency treatment should be available during testing, and patients should be kept under observation for at least 30 minutes after testing.

Variables Affecting Skin Testing

Skin prick and intradermal tests could be affected by (1) the site of testing, (2) age, (3) BMI, (4) medications, (5) allergen immunotherapy, (6) circadian and seasonal variations, (7) menstrual cycles, and (8) stress and anxiety.

1. *Site of Testing*: The skin tests may be performed on the back or on the volar

surface of the forearm. Specific locations on the back and forearms vary in reactive intensity. The upper back is more reactive than the forearm (57,87), but the clinical significance of the greater reactivity of the back is considered to be minimal. Furthermore, once performed on the arm, the patient can witness the positive skin test, which may assist in patient education. Tests should be performed 5 cm from the wrist and/or 3 cm from the antecubital fossae (48).

2. *Age*: Although people of all ages can be skin tested, skin reactivity has been demonstrated to be reduced in infants (<12 to 18 months of age) and the elderly (88,89), especially elderly women more than 65 years old (90).

3. *BMI*: A recent study has shown a positive correlation between increased BMI and skin response to histamine (91).

4. *Medications*: H_1 antihistamines reduce skin reactivity to histamine and allergens and thus as a general rule should be withheld for a period of time corresponding to three half-lives of the drug (92). Histamine (H2) antagonists also may blunt dermal reactivity, although this is usually not clinically significant (93,94). Other medications, such as tricyclic antidepressants and chlorpromazine, can block skin test reactivity for extended periods of time and may need to be avoided for up to 2 weeks before testing (95). Short courses of oral corticosteroids do not affect skin reactivity (96). Long-term systemic corticosteroid therapy may affect mast cell response; however, it does not appear to affect skin testing with airborne allergens (97,98). Applications of topical corticosteroid preparations may inhibit skin reactivity and should not be applied at the site of testing for at least 1 week before testing (99). Leukotriene antagonists were thought to affect skin test results. However, recent studies suggest that montelukast had no effect on measurements of skin prick test (SPT) and thus there is no need to discontinue the treatment prior to skin testing. (100,101). β-Agonists, theophylline, decongestants, cromolyn, and inhaled or nasal corticosteroids have no effect on skin reactivity.

5. *Immunotherapy*: Individuals who have previously received allergen immunotherapy can have diminished (but typically not absent) skin reactivity to allergens when repeat testing is performed (102–104).

6. *Circadian Rhythm and Seasonal Variation*: There are conflicting data whether cutaneous reactivity changes during the day (105,106). One study suggested circadian rhythms can affect skin reactivity differently in atopic

individuals compared to healthy controls (107). Testing during certain times of the year also may influence skin reactivity (108,109). These variations, however, are of no clinical significance.

7. *Menstrual Cycle*: Gender does not have any effect on the results of skin tests (89). However, in women, the phase of the menstrual cycle may influence skin-test results. One study indicated a significant increase in wheal and flare size to histamine on days 12 to 16 of the cycle, corresponding to ovulation and peak estrogen levels (110).

8. *Effect of Mental Stress and Anxiety*: Stress and anxiety have been shown to enhance and prolong the wheal response especially in young adults, possibly associated with higher Il-6 production. However the clinical significant of these findings is not clear at this point (111,112).

■ *IN VITRO* MEASUREMENT OF SPECIFIC IGE

In vitro procedures detect allergen-specific (sIgE) antibodies in the patient's serum. High-quality *in vitro* tests could be of use in multiple clinical scenarios, especially for demonstration of aeroallergen and food sensitivity (113–118). It is recommended that the total serum IgE level should be obtained together with serum-specific IgE measurements (119).

Although skin testing is the diagnostic test of choice for IgE-mediated disease, *in vitro* testing may be indicated in specific circumstances:

1. Because there are no medications that interfere with *in vitro* testing, this modality may be useful in patients who are unable to withhold medications with antihistamine properties.

2. In patients with a history of extreme sensitivity to allergens, use of *in vitro* tests would avoid uncomfortable local reactions associated with skin testing. Moreover, there is no risk of anaphylaxis with *in vitro* testing.

3. In patients who demonstrate dermatographism or have skin lesions affecting testing sites (i.e., forearm or back), *in vitro* testing *may be* preferable over skin testing.

4. In patients with unusually greater risk for anaphylaxis from skin tests (history of severe reactions or uncontrolled asthma) *in vitro* testing is preferable.

5. *In vitro* testing is also useful in patients who are unable to cooperate with skin testing.

The most predictive and most useful method of measuring sIgE is the Phadia

CAP system (Uppsala, Sweden), a fluoroenzyme immunoassay that has been approved for use by the U.S. Food and Drug Administration. This is a quantitative test with a reportable range of 0.1 to 100 kU$_A$/L. This assay, also referred to as ImmunoCAP, has been used in previous studies (118,120–122) to define diagnostic points for certain foods (123). These data curves have been generated for some of the more common food allergens, including egg, milk, peanut, and fish (118). The Radio Allergo Sorbent Test (RAST) is the colloquial term that refers to an antiquated *in vitro* method of measuring sIgE. Although this is no longer the method used in most laboratories, the term is still in use. Overall specific IgE levels appear sensitive but not specific for diagnosis of IgE-mediated food allergy (124). It is important to note that results may not be comparable between tests or between commercial laboratories. Additionally, malizumab may affect total and specific IgE results in different assays; however, total and specific IgE measured by the ImmuoCAP system are accurate in the presence of omalizumab (125).

Similar to the skin prick test, many published studies have attempted to correlate serum-specific IgE levels with results of food challenges to hopefully predict the likelihood that a patient will react on ingestion of food and thus abrogate the need for oral challenge (126–130).

The ratio of the specific IgE level to the total IgE level, as opposed to the specific IgE level alone, may be more accurate in predicting outcomes of food challenges (131).

It is important to note that higher sIgE levels do not correlate with severity of reactions but rather indicate an increased probability of a food-induced reaction. Therefore, the 95% predictive values are helpful in determining which patients are at higher risk of developing a reaction with ingestion and identifying those patients for whom oral challenges may not be advisable. On the other hand, there are limitations to this assay as patients (up to 20%, depending on the food) may react to a food despite very low or undetectable levels of food sIgE as demonstrated by oral challenges (118). Simply establishing the presence of sIgEs against allergens (sensitization), whether measured *in vivo* or *in vitro*, does not automatically designate disease or clinical relevance in a given patient. Among children who have elevated sIgEs to food as measured by ImmunoCAP, Perry et al. (132) demonstrated that those without a clear history of a food reaction were more likely to be tolerant to the food in double-blind placebo-controlled food challenges. Therefore, sensitization may be symptomatic (as in food allergy) or asymptomatic (as in food tolerance).

Therefore, as with skin prick testing, serum-specific IgE testing should not be used in isolation to diagnose food allergy. Diagnostic accuracy may increase with a combination of these two tests (126).

Component-Resolved Diagnostics

Recently, investigators have proposed assays to investigate the specific component of food proteins, allowing for better accuracy in diagnosing food allergy (133–136). These assays may also provide prognostic indicators for food allergies (137,138).

Findings of sIgE binding to specific component peptides may also correlate with more severe clinical reactions (134,135,139).

In contrast to foods, diagnostic values for *in vitro* tests have not yet been firmly established for aeroallergens. Some investigators consider serum-specific IgE to inhalants to be inferior and supplementary to skin tests (119).

As a rule, test results must correlate with allergic signs and symptoms from a specific antigen to have any meaning. Consequently, H&P carefully performed by the physician remains the fundamental investigative procedure for the diagnosis of allergic disease.

Provocation Tests

Although nasal or bronchial challenges with specific antigens to confirm immediate sensitivity are rarely performed in routine practice, they are nevertheless important tools in research studies. Nonspecific bronchial reactivity may be assessed with methacholine or histamine and is occasionally used to refute the diagnosis of asthma. Because positive methacholine challenges occur in patients with a variety of disorders, including allergic rhinitis, upper respiratory infections, chronic obstructive airway diseases, and sarcoidosis, as well as in smokers, the utility of confirming a diagnosis is limited (140).

Oral Food Challenges

Oral food challenges (OFCs) may be necessary in the diagnosis of food allergy. OFCs are performed on a regular basis in clinical practice for diagnosis and determination of tolerance. Double-blind placebo-controlled food challenges are the gold standard in the diagnosis of food allergy and may be required occasionally. Provocation testing should be performed in a medically supervised setting with emergency equipment and treatment readily available. Details can be found in Chapter 14.

Evaluation of Respiratory Function

Quantitative tests of ventilation by spirometry can be of great value in diagnosis of lower airways diseases and/or extra thoracic obstructive diseases. They may yield some insight into the type and severity of the functional defect and, more importantly, may provide an objective means for assessing changes that may occur with time or may be induced by treatment. These tests are detailed in Chapter 32. It must be remembered that single sets of values describe conditions at designated points in time, and conditions such as asthma have rapid pathophysiologic changes. A flow–volume loop may demonstrate extrathoracic obstruction such as vocal cord dysfunction that may mimic asthma symptoms. Guidelines recommend spirometry both for diagnosis and periodic monitoring of asthma (141). More extensive pulmonary function testing in a specialized pulmonary function laboratory may be necessary if the office spirometry is indeterminant or shows severe abnormalities.

Fractional Exhaled Nitric Oxide

Fractional exhaled nitric oxide (FeNO) is elevated in asthmatics and decreases after corticosteroid therapy and is a noninvasive measure of airway inflammation (142–144). FeNO has potential utility in managing asthma in terms of monitoring disease severity and adjusting anti-inflammatory therapy and is currently being utilized in research protocols as well as some clinical practices (145).

Other Laboratory Analyses

Total serum IgE is generally elevated in atopic individuals, especially patients with atopic dermatitis. However, concentrations fluctuate widely around a mean of 125 IU/mL (300 ng/mL) among atopic and nonatopic individuals (146–149). Serum total IgE has been found to be negatively correlated with measurement of lung function (150–152) and is used as a biomarker in asthma to guide therapy with anti-IgE monoclonal antibodies such as omalizumab (153).

Total serum IgE determinations are indicated in patients suspected of having allergic bronchopulmonary allergic aspergillosis, both in the diagnosis and monitoring of the course of the disease (154,155).

An extremely high IgE concentration is found in nearly all patients with allergic bronchopulmonary aspergillosis (ABPA) and is one of the major diagnostic criteria. IgE concentrations are also necessary in the evaluation of certain immunodeficiencies such as hyper-IgE (or Job's) syndrome.

Abnormalities of red cells or of the sedimentation rate are not associated with atopic disease. If such abnormalities are present, other illnesses or complications should be suspected. The differential white blood cell count is usually normal, with the frequent exception of eosinophilia that may range from 3% to 12%, especially in patients who have both atopic dermatitis and asthma. Higher eosinophil counts are not ordinarily seen in mild atopic diseases. The evaluation of eosinophilia is reviewed in Chapter 33. Extensive laboratory evaluation for urticaria and angioedema is generally not required and is not cost-effective (156–158).

Laboratory evaluation and further workup including skin biopsy is suggested by the history. See Chapter 13 for further details. Sputum Gram stain and culture aid in the diagnosis of some patients. Gross and microscopic findings in nasal secretions and in sputum have been described in allergic patients. These changes include eosinophils, Curschmann spirals, Charcot–Leyden crystals, and Creola bodies. Although these are interesting findings, their presence or absence may not be of diagnostic value.

Imaging

Chest radiographs may be necessary to rule out concomitant disease or complications of asthma. Chest radiographs in patients with asthma may reveal hyperinflation or bronchial cuffing; however, most often they are normal (159). The utility of chest radiographs prior to admission for acute asthma exacerbations is controversial but radiographs are often recommended since they have been reported to reveal clinically significant abnormalities in 15% to 34% of patients (160–162). A screening sinus computed tomography (CT) scan without contrast material may be required in the evaluation of upper airways of patients with chronic or recurrent sinus infections (163). Plain radiography has limited utility, because of the high false-positive and false-negative rates, whereas CT scans have a major role in evaluating chronic rhinosinusitis (163,164).

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Physiologic and Biologic Evaluation of Allergic Lung Diseases

RAVI KALHAN AND JANE E. DEMATTEE

◼ INTRODUCTION

Allergic and immunologic lung disease can be assessed through a variety of physiologic and biologic measurements. Physiologic measurements include comprehensive pulmonary function testing, such as forced spirometry, measurement of lung volumes, and determination of diffusing capacity. Peak expiratory flow measurement is easy to obtain and may serve as a useful surrogate for complete spirometric evaluation. Bronchoprovocation testing represents a combined physiologic–biologic approach to assessing airway hyperreactivity, and fraction of expired nitric oxide is a biologic test that correlates with the amount of eosinophilic inflammation in the airways. Finally, bronchoalveolar lavage fluid provides a window into the biologic make-up of lung inflammatory cells and can be used in the diagnosis of hypersensitivity pneumonitis (HP) and eosinophilic pneumonia (EP).

◼ PULMONARY FUNCTION TESTING

Components of Forced Spirometry

Forced spirometry is an important component of pulmonary function testing and the key component of the physiologic assessment of obstructive airways diseases. The American Thoracic Society (ATS)/European Respiratory Society (ERS) task force on the Standardization of Lung Function Testing assert several indications for spirometry including diagnosis and monitoring of diseases that affect lung function and determining prognosis or response to therapeutic interventions in those diseases (1). A forced spirometry contains the following components:

- The *forced vital capacity (FVC)* is the maximum amount of air exhaled with a maximal forced effort from total lung capacity (TLC).

- The *forced expiratory volume in 1 second (FEV1)* is the maximal volume of

air exhaled in the first second of the FVC maneuver.

- The *mean forced expiratory flow between 25% and 75% of the FVC (FEF25%–75%),* also termed the *maximum mid-expiratory flow* (MMEF), provides a measurement of expiratory flow during the middle phase of the FVC maneuver and provides a measure of small airways obstruction, albeit an inconsistent and nonspecific one, in individual patients (1,2).

With worsening obstructive airways disease, airflow at low lung volumes can become very slow, and it may be difficult for older patients, or those with severe airflow obstruction, to sustain a complete FVC maneuver. Some experts have therefore advocated the use of the *forced expiratory volume in 6 seconds (FEV6),* the volume of air exhaled in the first 6 seconds of the FVC maneuver, as a substitute for FVC (3,4). The *FEV1/FVC ratio* (*or FEV1/FEV6 ratio*) can be calculated from the above data and, when low, serves as one of the defining features of obstructive airways disease. A *flow-volume loop* is also constructed as a part of forced spirometry and when analyzed visually can reinforce the presence of airflow obstruction, provide an early indication of airflow obstruction when the FEV_1/FVC ratio is not yet reduced, and provide information regarding extrathoracic (upper airway) obstruction.

PEF is the maximum expiratory flow achieved from a forced expiration starting, without hesitation, from TLC. *Reversibility testing* can be obtained as a part of forced spirometry by repeat testing after administration of a bronchodilator. Patients are considered to have reversible airflow obstruction when, following the administration of a bronchodilator, the FEV_1 and/or FVC increases by more than 12% *and* 200 mL in a single testing session. Repeat spirometry should be performed 10 to 15 minutes after administration of a short-acting β-agonist or 30 minutes after administration of a short-acting anticholinergic (2). Increases of <8% in FEV_1 or FVC are related likely to normal variability of the test and do not represent significant responses to a bronchodilator (5).

The FVC maneuver has three phases: maximal inspiration to TLC from relaxed breathing, a forced exhalation, and continued complete exhalation until the end of the test. Because false reductions in FEV_1 and PEF have been observed when the maximal inspiration is slow or there is a prolonged pause at TLC (6), the initial inspiration should be fast and pauses at TLC minimized. For an accurate FVC maneuver, specific criteria for the end of the test are essential. The volume–time curve should show no change in volume for 1 second or

greater, and the patient should have tried to exhale for 3 seconds or longer if younger than 10 years old or 6 seconds or longer if 10 years or older (7). In summary, an adequate FVC maneuver must have a maximum inspiration, a rapid start followed by a smooth continuous exhalation, and maximal effort until the volume–time curve reaches a plateau. Idealized flow-volume loops and volume–time curves are shown in Fig. 9.1.

Spirometry in Asthma

The Global Initiative for Asthma (GINA) recommends the use of forced spirometry in asthma at the following time periods (8):

1. When the diagnosis of asthma is being considered (at the time of initial evaluation).

2. At the start of treatment, 3 to 6 months after starting controller treatment, and then periodically (in the current authors' clinical program, we assess spirometry every 1 to 2 years to monitor airway function as recommended by the National Asthma Education and Prevention Program (NAEPP) of the U.S. National Heart, Lung, and Blood Institute) (3).

3. Before treatment is initiated for acute exacerbation (if feasible) and then at 1 hour intervals thereafter until there is improvement or a plateau.

Although clinical symptoms are important factors in diagnosing asthma, symptoms often do not correlate well with lung function in either adults or children (9–12), creating a well-documented disconnect between severity of asthma symptoms and severity of airflow obstruction (13).

Airflow obstruction that is spontaneously reversible or reversible with medical intervention on forced spirometry is a principal clinical feature of asthma (3). The ATS/ERS task force defines an obstructive ventilatory defect as occurring when there is a disproportionate reduction of *maximum airflow* relative to *maximum volume* (i.e., FVC) that can be displaced from the lung (2). Obstructive defects are identified on spirometry by a reduction in the FEV_1/FVC ratio. The National Health and Nutrition Examination survey (NHANES III)-derived reference equations (14) provide ethnically appropriate predicted values for the FEV_1/FVC ratio and other spirometric parameters. The ATS/ERS task force suggests that obstruction is present when an individual's FEV_1/FVC ratio is below the fifth percentile of the predicted value or alternatively when it is less than the lower limit of normal (LLN) based on the reference equations (2). While in small airways obstruction the $FEF_{25\%-75\%}$ can be reduced as well, and often

this occurs earlier in disease than a decrease in the FEV_1, abnormalities in MMEF are not specific for small airways disease and should not be used to identify airflow obstruction (2).

After identifying the presence of an obstructive defect in patients in whom there is clinical suspicion of asthma, assessment of bronchodilator responsiveness is appropriate. The GINA statement notes that asthma is a variable disease characterized by daily, monthly, or seasonal variation in symptoms and lung function (8). The variability that is an essential feature of asthma results in a variable response in an individual patient to bronchodilator testing. An individual patient is unlikely to exhibit bronchodilator responsiveness every time he or she is tested, particularly if the disease is well controlled (8). Repeated testing at different times, therefore, is important to confirm the diagnosis of asthma as well as assess asthma control (3,8).

After an FEV_1/FVC ratio less than the LLN is detected by spirometry, the ATS/ERS task force recommends that the severity of airflow obstruction be assessed by the magnitude of reduction in the FEV_1.

- Mild obstruction—FEV_1 > 70% predicted, but below LLN

- Moderate obstruction—FEV_1 60% to 69% predicted

- Moderately severe obstruction—FEV_1 50% to 59% predicted

- Severe obstruction—FEV_1 35% to 49% predicted

- Very severe obstruction—FEV_1 < 35% predicted

Obstructive ventilatory defects are visually detected by a delayed plateau on the volume–time curve as well as "scooping," "coving," or upward concavity to the shape of the expiratory limb of a flow–volume curve (Fig. 9.2). The inspiratory limb of the flow–volume loop is normal in asthma. If the inspiratory limb is flattened, extrathoracic causes of airflow obstruction should be considered. Vocal cord dysfunction (VCD) can clinically mimic asthma and has been reported to be concomitant with asthma in many patients (15). When asthma symptoms persist despite therapy, a flattening of the inspiratory limb of the flow loop, termed *variable extrathoracic obstruction*, can prove useful in raising suspicion of VCD as an etiology of persistent symptoms.
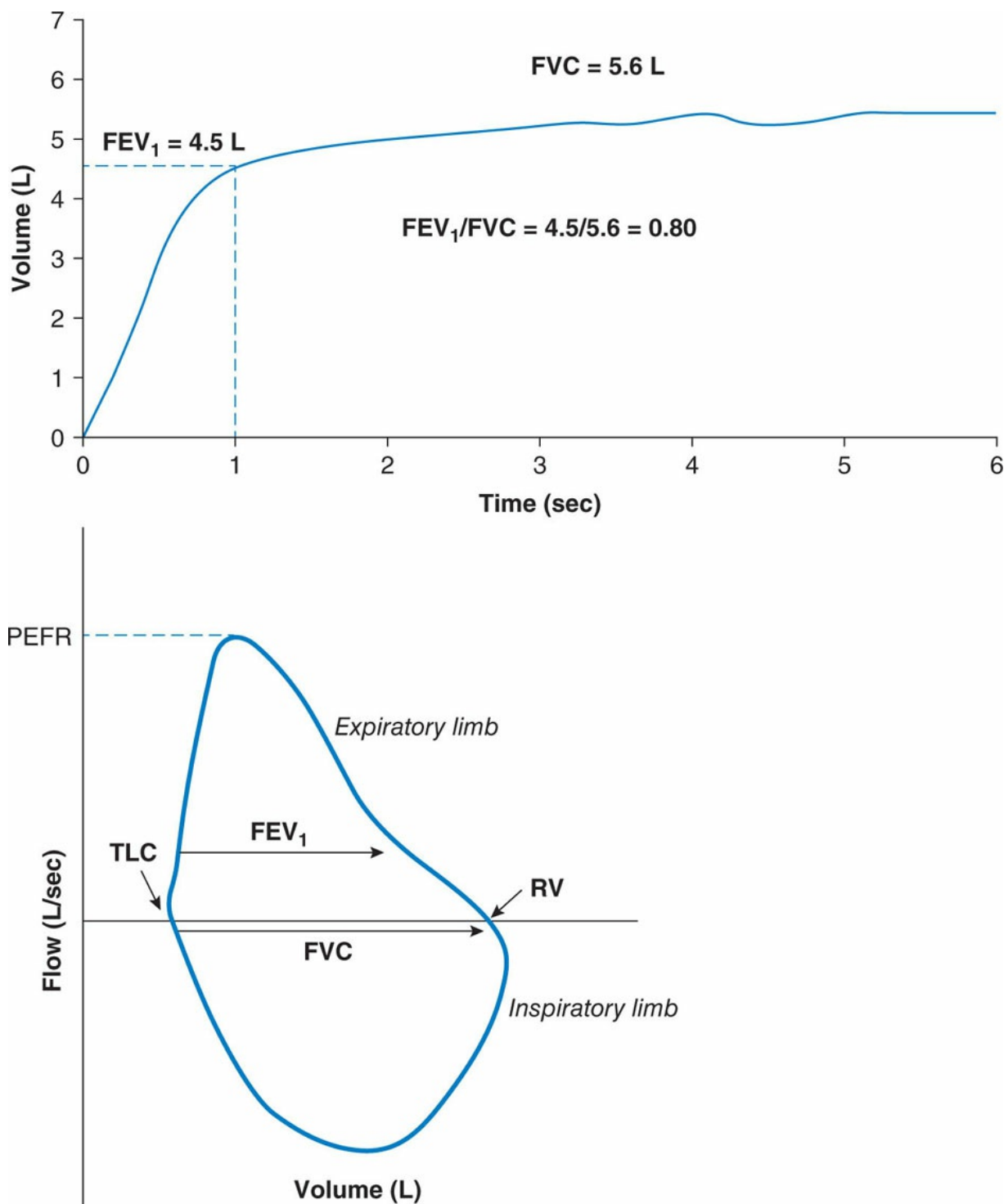
FIGURE 9.1 Stereotypical volume–time curve **(top)** and flow–volume loop **(bottom)** in a normal subject. In the volume–time curve, approximately 80% of volume is expired in the first second resulting in a normal FEV_1/FVC ratio of 0.80. The quality of the maneuver is documented by a volume-plateau at the termination of the test after 6 seconds. After inspiration to total lung capacity (TLC), the expiratory limb of the flow–volume loop has a sharp increase in peak expiratory flow rate (PEFR) and then a smooth deceleration in flow over the

entire expiration until complete at residual volume (RV). FEV^1, forced expiratory volume in 1 second; FVC, forced vital capacity.

The NAEPP recommends periodic spirometry in addition to assessing symptoms (3) because individuals with low FEV_1 represent a group at high risk for acute asthma exacerbations (16). The frequency of performing spirometry in an individual patient depends on whether he or she does not perceive symptoms until airflow obstruction is severe. Unfortunately, there is no good means for detecting these "poor perceivers" (3). It has been documented that in some asthma patients, there is little correlation between FEV_1 and self-perception of severity of airflow obstruction (17). This inability to perceive severity of airflow obstruction among some patients, coupled with the fact that many patients with near-fatal asthma are in fact "poor perceivers" (18), makes regular spirometry testing an important aspect of disease monitoring.
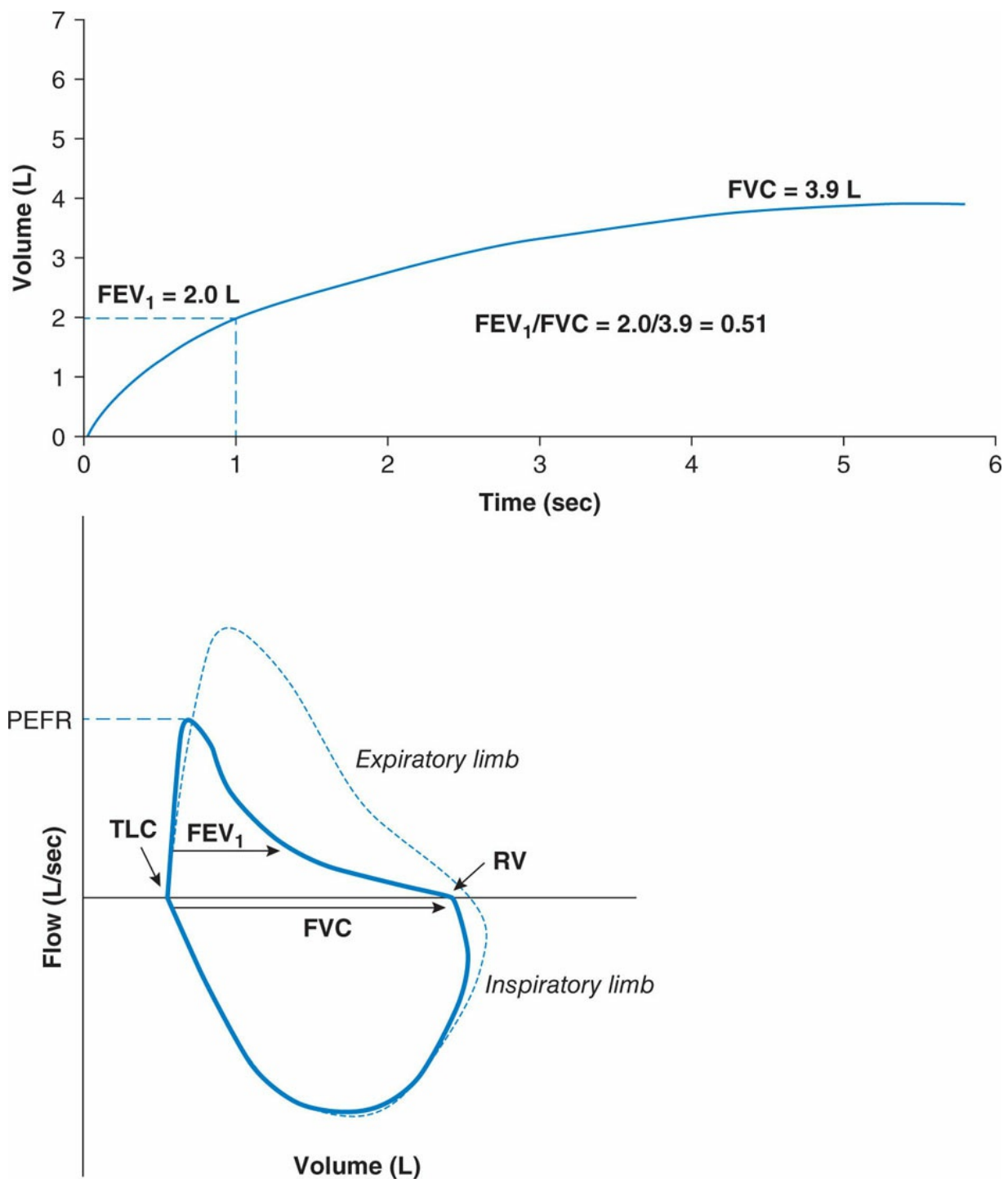
■ **FIGURE 9.2** Volume–time curve **(top)** and flow–volume loop **(bottom)** in obstructive airways disease such as asthma. On the volume–time curve, note that only approximately 50% of volume is expired in the first second resulting in a decreased FEV_1/FVC ratio of 0.51. In addition, the plateau of expired volume is delayed and not achieved until later in the expiratory maneuver compared with the example in Figure 9.1, but a plateau is still achieved at 6 seconds indicating a test of adequate quality. The flow–volume loop shows a decreased PEFR compared to normal (*dashed curve*), and the expiratory curve demonstrates the

characteristic concave upward (or "scooped") appearance reflecting decreased expiratory flow throughout the maneuver. FEV^1, forced expiratory volume in 1 second; FVC, forced vital capacity.

■ PEAK EXPIRATORY FLOW RATE

Handheld peak-flow meters serve as a convenient tool for monitoring lung function in asthma. They are not, however, diagnostic tools for the presence of airflow obstruction, and it is recommended that patients who monitor PEFRs have yearly correlation with FEV_1 performed to check the accuracy of the peak flow meter (3,19). PEFR is dependent on patient effort, and is an adequate inspiration to TLC before initiating the maneuver. After inhaling to TLC, the patient should deliver a maximal expiratory blow without any hesitation and with the neck in a neutral position. Hesitation before the forced blow, neck flexion, spitting, and coughing diminish the accuracy of the PEFR measurement (1). When PEFR monitoring is used in clinical practice, initial teaching, followed by regular evaluations of the patient's technique, is appropriate. The NAEPP report recommends consideration of long-term home peak-flow monitoring when patients

- have moderate or severe persistent asthma;

- have a history of severe asthma exacerbations;

- are "poor perceivers" of airflow obstruction;

- prefer this method of monitoring asthma.

PEFR, when placed in the context of a patient's "personal best" PEFR, can be used to diagnose, understand the severity of, and evaluate the rate of resolution of an asthma exacerbation. Results of the utility of PEFR monitoring have been inconsistent in clinical studies, and the decision to use this modality of monitoring should be made on a case-by-case basis (1,20).

■ BRONCHOPROVOCATION TESTING

Although methacholine is the most common agent used in bronchoprovocation testing, challenge testing may be performed with a variety of stimuli including cold air, histamine, or exercise. Bronchoprovocation testing is indicated when asthma is suspected clinically, but spirometry is normal (3). When performing bronchoprovocation testing, clinicians should remain mindful that a positive methacholine bronchoprovocation test (MCT) is diagnostic of the presence of bronchial hyperresponsiveness (BHR), which may be present in a variety of

conditions (chronic obstructive pulmonary disease, allergic rhinitis, and congestive heart failure among others) including asthma (21). In a typical MCT, dilute concentrations of methacholine are given via a dosimeter and nebulizer system and serial spirometric measurements made. In the recommended methacholine dosing protocol, increasing concentrations of methacholine are delivered serially, and after each inhalation, an FEV_1 is measured within 90 seconds. The test is terminated when the FEV_1 declines by 20%, a measurement termed the *provocative concentration* 20% (PC_{20}) to methacholine (21). The test is deemed negative if the FEV_1 has not declined by >20% after the highest dose of methacholine (16 mg/mL) is delivered (21). The ATS suggests the following interpretation of MCT (21):

- PC_{20} > 16 mg/mL—normal bronchial responsiveness

- PC_{20} 4 to 16 mg/mL—borderline BHR

- PC_{20} 1 to 4 mg/mL—mild BHR (positive test)

- PC_{20} < 1.0 mg/mL—moderate to severe BHR

Because BHR is not specific to asthma, bronchoprovocation testing may have more utility in excluding asthma than in actually confirming a diagnosis (3).

There are some implicit challenges associated with the use of PC_{20} as the defining feature of BHR that have become relevant as the English-Wright nebulizer, used to develop the validated delivery protocol, is no longer available. Many newer nebulizers are breath-actuated and deliver aerosols more efficiently (22). Data suggest that the provocative dose 20% (PD_{20}) results in better agreement when MCT are performed using nonvalidated nebulizers because differences in nebulizer output can be accounted for by calculating delivered dose. Use of PC_{20} in the setting of more efficient nebulizers will result in a higher false positive rate (23). Furthermore, the concept of cumulative dose when determining PD_{20} allows for a shorter dose delivery time of methacholine with more efficient nebulizers, wherein the inhalation inducing BHR may be influenced by the effects of prior inhalations. The delivered dose of methacholine at a given concentration requires knowledge of rate of output for a given nebulizer, the inhalation time, and the concentration being used. In a study comparing the obsolete English-Wright nebulizer with 2-minute inhalation to a modern breath-actuated nebulizer requiring only 30 seconds of inhalation, the PD_{20} was directly comparable, whereas the PC_{20} was not (23). Protocols for

MCT using a newer nebulizer have been studied in both children and adults (22,23). Whether guidelines are adapted to recommend the use of either PC_{20} or cumulative PD_{20} when defining BHR remains to be seen at the time of this writing.

FRACTION OF EXHALED NITRIC OXIDE

Nitric oxide (FE_{NO}) is a noninvasive marker of eosinophilic airway inflammation (24–26) with potential utility in monitoring asthma (3). FE_{NO} is elevated in asthma patients never treated with steroids (27,28), and decreases following treatment with inhaled steroids (25). The magnitude of FE_{NO} may be a useful predictor of steroid responsiveness (29). A commercially available system that provides instantaneous FE_{NO} measurement has been approved by the U.S. Food and Drug Administration for monitoring asthma (30).

Because of the correlation of FE_{NO} with eosinophilic airways inflammation and its potential predictive power in determining steroid responsiveness, recent studies have attempted to use FE_{NO} to guide therapy with inhaled corticosteroids and determine asthma control. The results of studies using FE_{NO} to guide therapy have been inconsistent (31,32). Two studies have indicated that FE_{NO} may be helpful as a marker of asthma control (33,34) with the test having particular utility in patients treated with low doses of inhaled corticosteroids (34). Several issues remain before FE_{NO} becomes routine clinical practice including a better understanding of normal and abnormal cut-point values and a determination of the minimally important clinical difference for a FE_{NO} reduction.

Components of Lung Volume Testing

Full pulmonary function tests (PFTs) comprise measurement of absolute lung volumes and diffusing capacity in addition to forced spirometry. Absolute lung volumes include: *residual volume (RV),* the volume of gas that remains in the lung after a complete expiration; *functional residual capacity (FRC),* the volume of gas remaining in the lung after exhaling a normal tidal breath; and *TLC,* the maximal amount of gas in the lung after maximal inspiration (Fig. 9.3). Lung volumes are typically measured by plethysmographic, helium gas dilution or nitrogen washout methods. Body plethysmography is considered the optimal method because both ventilated and nonventilated lung volumes are measured. A discussion of the methodology used to measure lung volumes is beyond the

scope of this chapter but was published by the ATS/ERS task force (35).

Measurement of lung volumes is required for the definitive diagnosis of a restrictive ventilatory impairment, defined as a reduction of the TLC below the fifth percentile of the predicted value (2). A restrictive pattern on PFTs suggests the presence of parenchymal lung disease wherein there is concentric reduction in all volumes, the TLC, FRC, RV, and VC. Severity of the restrictive impairment is based on the degree of reduction in the TLC as set forth by the ATS in 1991 (36).

- Mild restriction—TLC > 70% predicted <LLN

- Moderate restriction—TLC 60% to 69% predicted

- Moderately severe restriction—TLC 50% to 59% predicted

- Severe restriction—TLC 34% to 49% predicted

- Very severe restriction—TLC < 34% predicted

A significant drawback to lung-volume testing is the lack of robust reference standards. The studies from which lung-volume reference values were derived are obsolete, lack standardized and detailed description of measurement technique, included asymptomatic smokers, had small sample sizes, and were Caucasian-based and cannot be directly applied to other ethnic groups (37). Lung volumes should be adjusted for ethnicity when race-based reference values are not available (2,38).

Measurement of Diffusing Capacity

The *diffusing capacity (DLCO)* measures the capacity of the lung to exchange gas across the alveolar capillary interface and is most commonly measured by a determination of carbon monoxide (CO) uptake from the lung in a single breath technique. The diffusing capacity is dependent on a number of factors including the thickness of the alveolar capillary membrane, the intact surface area between the alveoli and capillary, which is dependent on the lung gas volume and thoracic blood volume at which DL_{CO} is measured, the matching of ventilation and perfusion, and the hemoglobin concentration available for CO binding (39). Thus, many factors have the ability to alter the measured DL_{CO}. The technique to measure the DL_{CO} was reviewed by the ATS/ERS task force (39). Severity of the diffusing impairment is based on the extent of the reduction in the DL_{CO} as set forth by the ATS/ERS task force (2).
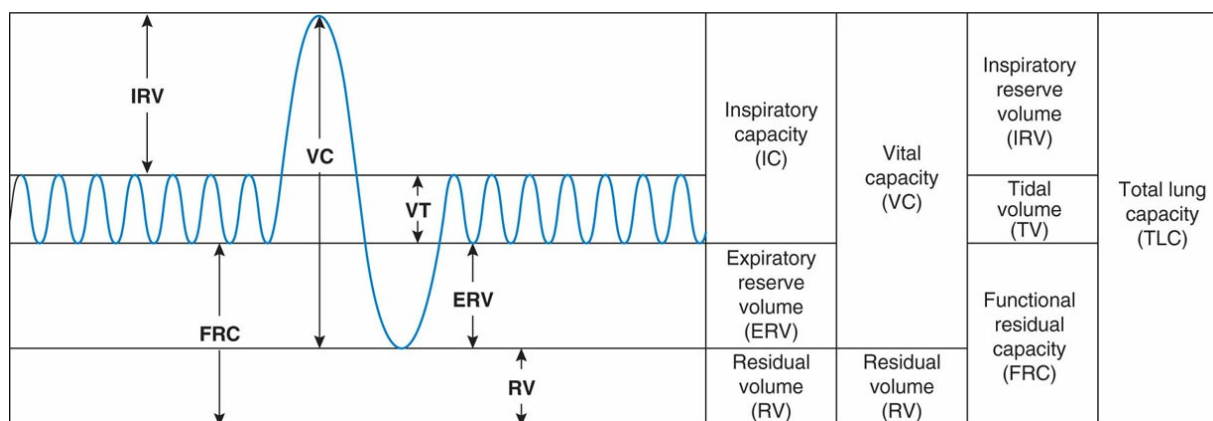
■ **FIGURE 9.3** Residual volume (RV): the volume of gas that remains in the lung after a complete expiration; functional residual capacity (FRC): the volume of gas remaining in the lung after exhaling a normal tidal breath; total lung capacity (TLC): the maximal amount of gas in the lung after maximal inspiration; inspiratory capacity (IC): the difference between TLC and FRC; expiratory reserve volume (ERV): the difference between FRC and RV.

- Mild impairment—DL_{CO} > 60% predicted <LLN

- Moderate impairment—DL_{CO} 40% to 60% predicted

- Severe impairment—DL_{CO} < 40% predicted

Lung Volumes and DL_{CO} in Asthma and Other Obstructive Airway Diseases

Lung-volume measurements are essential to discriminate between obstructive and restrictive impairment when spirometry indicates reductions in both the FEV_1 and FVC. In moderate and severe obstruction, air trapping and hyperinflation may lead to a reduction in the FVC and a deceptively normal FEV_1/FVC ratio. The diagnosis of obstruction can be overlooked in this setting unless lung-volume measurements are performed. The presence of a normal or increased TLC or RV would confirm the presence of airflow obstruction. The FEV_1 can be used to gauge the severity of disease; however, the FEV_1/FVC ratio is not useful in this setting. Increases in the TLC and RV indicate the presence of gas trapping, loss of elastic recoil, and hyperinflation in severe obstruction and emphysema and can be important indicators of disease severity (40,41).

The DL_{CO} is useful in discriminating among forms of obstructive lung diseases. In patients with a concomitant history of asthma and tobacco abuse, the

DL_{CO} is the best means by which to distinguish between asthma and chronic obstructive pulmonary disease/emphysema. In asthma, DL_{CO} should be normal or elevated (42), whereas the DL_{CO} will be reduced in the presence of emphysema (43).

Pulmonary Function Testing in Restrictive Lung Diseases

Forced spirometry, when performed in restrictive diseases, is characterized by the presence of a normal or increased (>85%) FEV_1/FVC ratio and a diminished FVC (2). In the setting of restrictive lung disease, the flow-volume loop is often narrowed and the expiratory limb has a convex upward shape (2). This spirometric pattern lacks specificity for restrictive lung disease and can be associated with poor patient effort on the forced spirometry. A low FVC, therefore, cannot be deemed diagnostic of a restrictive ventilatory defect and measurement of lung volumes and diffusing capacity is required. A diminished FVC carries a positive predictive value for an actual restrictive ventilatory defect of only 41% (44,45). The negative predictive value for an FVC in excluding a restrictive defect, however, is 97.5% (44). Therefore, forced spirometry may serve as a useful screening tool to exclude restrictive lung diseases. Once a restrictive impairment has been established by lung volume measurements, spirometric measure of FVC can be used to monitor progression of disease and response to treatment (46). Measurement of lung volumes is also required to establish a mixed obstructive and restrictive impairment.

Pulmonary Function Tests in Allergic Lung Disease

Hypersensitivity Pneumonitis

PFTs alone are rarely helpful in establishing a diagnosis of, or in classifying, HP; however, they are useful in quantifying the extent of disease and monitoring response to exposure avoidance and/or treatment. In its stereotypical acute form, HP demonstrates a prevailing pattern of a restrictive ventilatory defect on pulmonary function testing, whereas in subacute or chronic HP, obstructive and mixed patterns are common (47–50). A restrictive pattern correlates with ground-glass infiltrates and reticulation on chest computed tomography (CT). Obstructive patterns, which include decreased FEV_1, decreased MMEF, and air trapping, correlate with areas of decreased attenuation and bronchiolitis on chest CT (50,51). In chronic HP, emphysematous changes are also seen on chest CT scans and correspond with obstructive patterns on PFTs (48). Patients with HP related to farmer's lung demonstrate airflow obstruction and gas trapping after

acute exposure to antigen and airway hyperreactivity to methacholine (52). Regardless of the pattern of impairment, the DL_{CO} is often reduced (47,48) in HP. In early, acute forms of the disease, an isolated reduction in DL_{CO} may be the only abnormality detected (48). PFTs may be normal in early, mild disease (53).

In patients with acute or subacute HP, the PFT abnormalities are reversible with removal from exposure and/or treatment. In subacute disease, abnormalities may be intermittent corresponding to exposure, but may become chronically progressive. In chronic HP, the impairment in pulmonary function is irreversible (48,50,54,55).

Idiopathic Eosinophilic Pneumonia

PFT data in EP are limited but most studies describe abnormalities in the majority of patients. The pattern of impairment on presentation may be either obstructive or restrictive; mixed patterns are rarely seen (56–59). Idiopathic chronic EP (ICEP) is often associated with underlying asthma and although obstruction is more common in those with a history of asthma, it was also seen in those without this preexisting diagnosis. The presence of obstructive impairment is consistent with extension of eosinophilic inflammation to the distal airways (57). Abnormalities in DL_{CO} are also found in the majority of patients (57,60). In ICEP, pulmonary function tests normalized rapidly with treatment; however, long-term follow-up demonstrated an obstructive impairment in a high percentage of patients, some of whom had fixed disease (56,57). Those with underlying asthma often experienced worsening of symptoms (61).

Idiopathic acute EP (IAEP) is also associated with abnormal PFTs, most often with small airway disease, as evidenced by reduced mid- and low lung volume flows, but mild restrictive impairment is also reported. DL_{CO} is reduced in nearly all patients and hypoxemia is common at presentation (62,63). PFTs return to normal with treatment in most patients (62–64); however, residual restriction has been reported (63).

◼ BRONCHOALVEOLAR LAVAGE FLUID CELLS IN ALLERGIC LUNG DISEASE

Analysis of bronchoalveolar lavage fluid (BALF) provides important, and often diagnostic, information in allergic lung diseases. In health, macrophages predominate in BALF constituting 89% of cells in nonsmokers. Lymphocytes account for 9%; most are T-cells with a CD4:CD8 ratio averaging 1.9 (±1).

Neutrophils make up 1% of BALF cells (65,66).

BALF in Hypersensitivity Pneumonitis

In contrast to healthy subjects, BALF in patients with HP demonstrates a lymphocytic alveolitis (67). The percentage of lymphocytes is higher in subacute disease as compared with chronic disease (in one study, 53% versus 38% respectively). Furthermore, lymphocytes are more abundant in patients without radiographic evidence of fibrosis, 59% compared with 20% in those with fibrosis (68). Neutrophils are also present in a higher percentage (48,49) and may be the predominant cell in early acute HP (69). BALF lymphocytosis is more sensitive for the diagnosis of early and/or mild HP wherein both high-resolution chest CT and PFTs may be normal (53). A lymphocyte percentage of <30% in the BALF makes the diagnosis of HP less likely (49).

While the lymphocytes are predominantly T-cells, the prevalent T-cell phenotype is less clear. Numerous studies have demonstrated either an increase in CD8 cells with a CD4/CD8 ratio of <1 (55,70) or an increase in CD4 cells with a ratio >1 (67). The observed variation may be because of the time taken from antigen exposure until sampling. A predominant CD8$^+$ lymphocytosis may be found in the acute stage of disease but shifts to the predominant CD4$^+$ at a quiescent stage after antigen avoidance (71–73). The type of antigen may also be important in determining the phenotypic response (74). A marked predominance of CD4$^+$ cells is seen in mycobacterium avian complex–associated HP with CD4/CD8 ratios ranging from 6 to 49 (47,75). Similarly, HP in pigeon breeder's lung is associated with an increased CD4/CD8 ratio, whereas summer–type HP is associated with a decreased CD4/CD8 ratio (74,76).

BALF in Eosinophilic Pneumonia

BALF analysis is also useful in the diagnosis of eosinophilic lung disease. Measurement of eosinophils in the alveolar space has nearly replaced lung biopsy for diagnosis of EP. Normally eosinophils account for <2% of cells in the BALF (66), counts between 2% and 25% are nonspecific and are found in diseases such as asthma or eosinophilic bronchitis; however, counts >25% are seen in IAEP and >40% in ICEP (57,61,63).

In patients with IAEP, the eosinophils are atypical with few granules and greater than two nuclear lobes. Eosinophils decrease to <1% of BALF cells on post–treatment analysis (63). Although blood eosinophilia is uncommon at presentation of IAEP (62–64), it is common in ICEP. The combination of blood

and BALF eosinophilia can provide a noninvasive diagnosis in the proper clinical setting. Although ICEP is also associated with increased BALF lymphocytes, eosinophils are always more abundant than lymphocytes, which is useful in distinguishing it from other diseases (56,57,64).

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Radiologic Evaluation of Allergic and Related Diseases of the Upper Airway

ERIN N. MCCOMB, MICHELLE J. NAIDICH, ERIC J. RUSSELL, AND ACHILLES G. KARAGIANIS

INTRODUCTION

The anatomy of the sinuses can be viewed in two separate but interrelated groups: the sinuses themselves and their associated outflow tracts. There are paired frontal and maxillary sinuses, paired anterior and posterior ethmoid air cells, and a paired sphenoid sinus. Some radiologists consider the sphenoid sinus to be a single sinus subdivided by a sphenoid septum. There are three main outflow tracts for the paranasal sinuses: the ostiomeatal complex, the sphenoethmoidal recess, and the frontoethmoidal (frontal) recess (Fig. 10.1). The sinuses all eventually drain into the nasal cavity.

The nasal cavity is divided vertically by the nasal septum. The anterior portion of the septum is cartilaginous (quadrangular cartilage), and the osseous posterior portion is comprised of the vomer inferiorly and the perpendicular plate of the ethmoid bone superiorly. The nasal vestibule is a paired air passage at the level of the nasal ala. The piriform aperture is the osseous opening to the nasal cavity. The nasal cavity communicates posteriorly with the nasopharynx via the nasal choanae (Fig. 10.2). The floor of the nasal cavity consists of the hard palate (anteriorly) and the soft palate (posteriorly) (1–4). There are typically three paired sets of inferiorly directed bony and cartilaginous projections in the nasal cavity. These are termed the *superior, middle*, and *inferior turbinates* (Fig. 10.2).

The basal lamella is a thin osseous plate that arises from the middle turbinate and has several attachments. The vertical portion of the basal lamella attaches to the cribriform plate superiorly (Fig. 10.3); the middle and posterior portions attach to the lamina papyracea laterally; and the posterior margin attaches to the palatine bone (5). The significance of the basal lamella is that it anatomically separates the anterior ethmoids from the posterior ethmoids.

The ostiomeatal complex (OMC or ostiomeatal unit) comprises the primary functional drainage unit for the maxillary sinuses, frontal sinuses, and anterior ethmoid air cells. This region has several components, including the primary (internal) maxillary sinus ostium, infundibulum, uncinate process, ethmoid bulla, hiatus semilunaris, and the middle meatus (Fig. 10.1) (1,3).

Mucus secretions, trapped dust particles, and inflammatory cells in the maxillary sinus are propelled centripetally by pseudostratified columnar ciliated epithelium (1,2). The cilia beat in a synchronous manner, directed superomedially toward the primary maxillary sinus ostium. If the sinus secretions become lodged in the OMC, post-obstructive sinus disease ensues (Fig. 10.4). Because of this pathophysiology, functional endoscopic sinus surgery (FESS) is most often performed to expand this ostium and the remainder of the OMC. Indeed, any surgery neglecting the primary maxillary sinus ostium in the setting of an OMC obstruction invariably fails in adequately treating the patient. This was seen years ago in patients who received a Caldwell–Luc surgery to treat sinus inflammatory disease. A Caldwell–Luc procedure used to be a common surgery performed for sinus inflammatory disease prior to the current understanding of the normal OMC physiology (Fig. 10.5). With this procedure, a hole was drilled in the anterior wall of the maxillary sinus and a nasal antral window was created in an effort to allow sinus secretions to drain via gravity into the nasal cavity. Unfortunately, this did not address the OMC and was prone to failure.
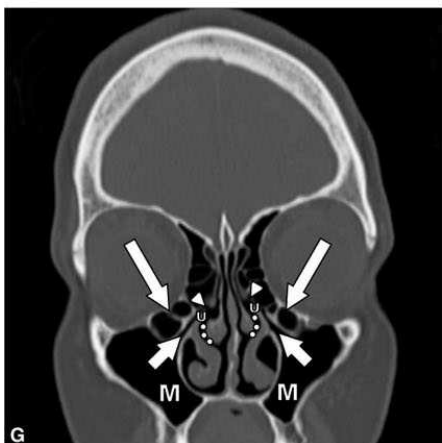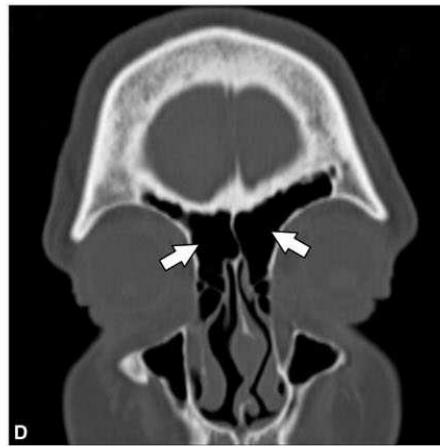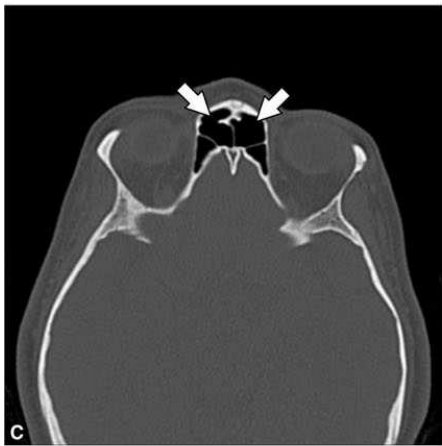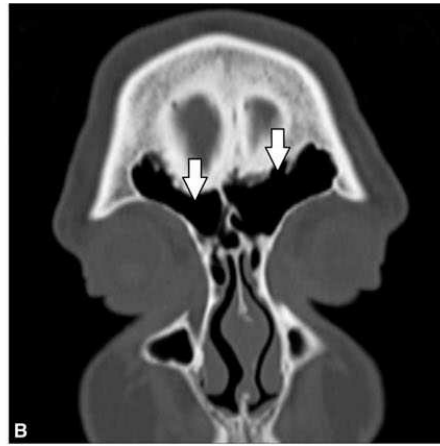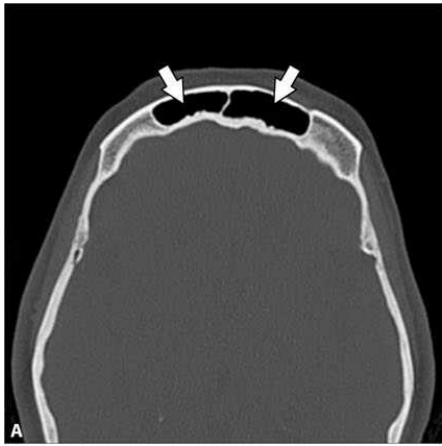
■ **FIGURE 10.1** Normal sinus anatomy. All of the following are computerized tomography (CT) images viewed with a bone window in either an axial or a coronal plane. Axial **(A)** and coronal **(B)** images demonstrate the frontal sinuses (*small arrows*). An axial image **(C)** slightly more caudal from image **A** demonstrates the frontoethmoidal recesses (*small arrows*). Coronal **(D)** and sagittal **(E)** images also demonstrate the frontoethmoidal recesses (*small arrows*). Axial **(F)** image demonstrates the anterior ethmoid air cells (*medium arrows*) and posterior ethmoid air cells (*small arrows*), the sphenoethmoidal recesses (*arrowheads*), and the sphenoid sinuses (*large arrows*). A coronal image **(G)** best demonstrates the ostiomeatal complexes including the infundibula (*small arrows*), uncinate processes (*U*), hiatuses semilunaris (*arrowheads*), and middle meatuses (*dots*). Haller cells are present bilaterally (*medium arrows*). The maxillary sinuses (*M*) drain into the ostiomeatal complexes.
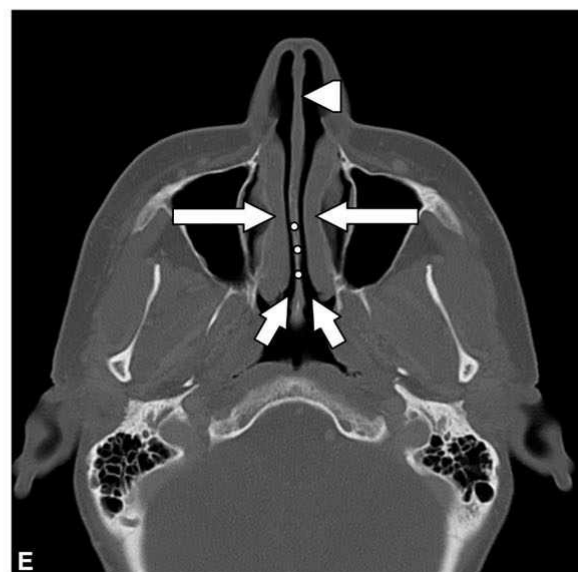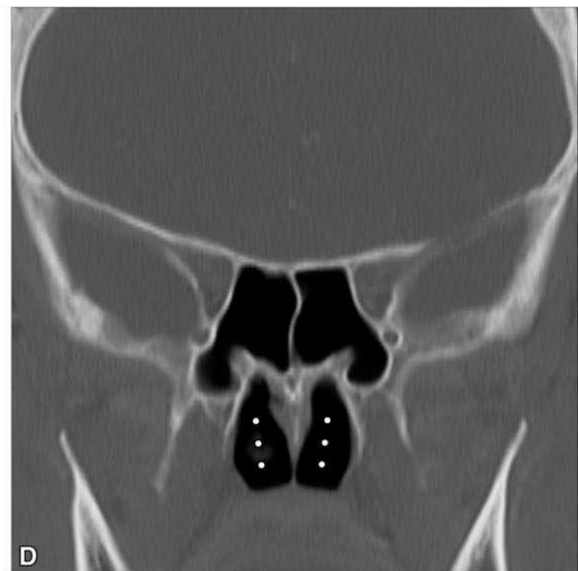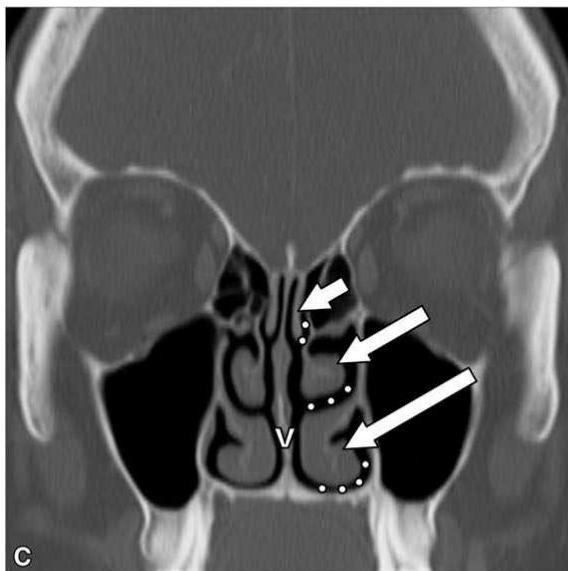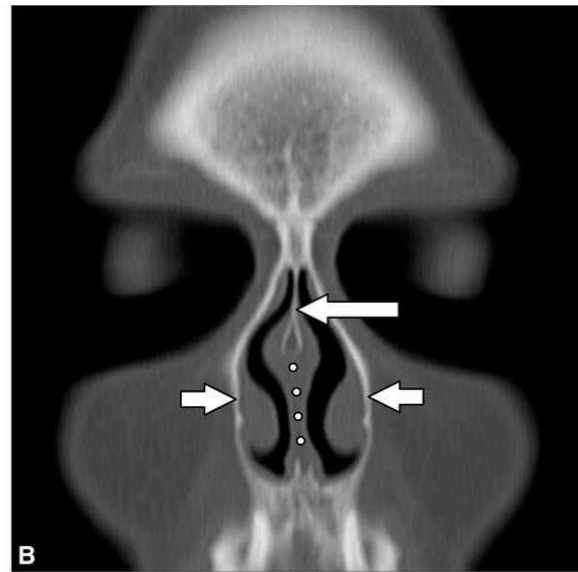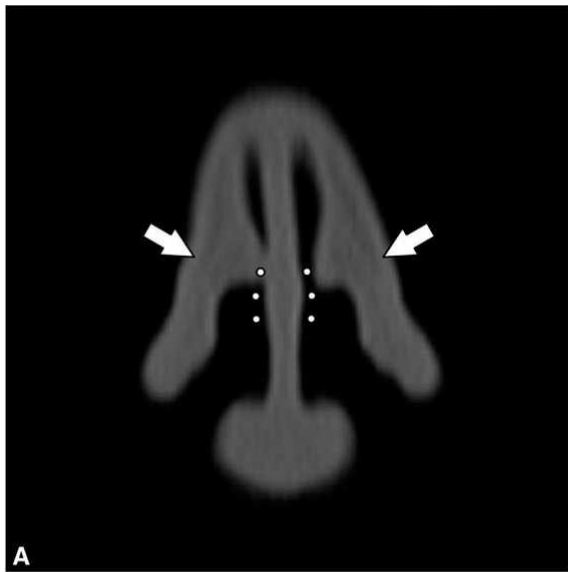
FIGURE 10.2 Normal nasal cavity anatomy. All the following images are CT

images viewed with a bone window in either an axial or a coronal plane. Coronal CT image **(A)** demonstrates the nasal ala (*small arrows*) and the nasal vestibule (*dots*). Coronal CT image **(B)** slightly more posterior to **A** demonstrates the perpendicular plate of the ethmoid (*medium arrow*), the cartilaginous portion of the nasal septum (*dots*), and the piriform aperture (*small arrows*). Coronal CT image **(C)** slightly more posterior to **B** demonstrates the superior (*small arrow*), middle (*medium arrow*), and inferior (*large arrow*) turbinates as well as the vomer (*V*). The superior, middle, and inferior meatuses are located below their respective turbinates (*small dots*). Coronal CT image **(D)** is located slightly more posterior to **C** and demonstrate the nasal choanae (*dots*). Axial image **(E)** at the level of the inferior turbinates (*medium arrows*) demonstrates the cartilaginous portion of the nasal septum (*arrowhead*), the vomer (*dots*), and the nasal choanae (*small arrows*).
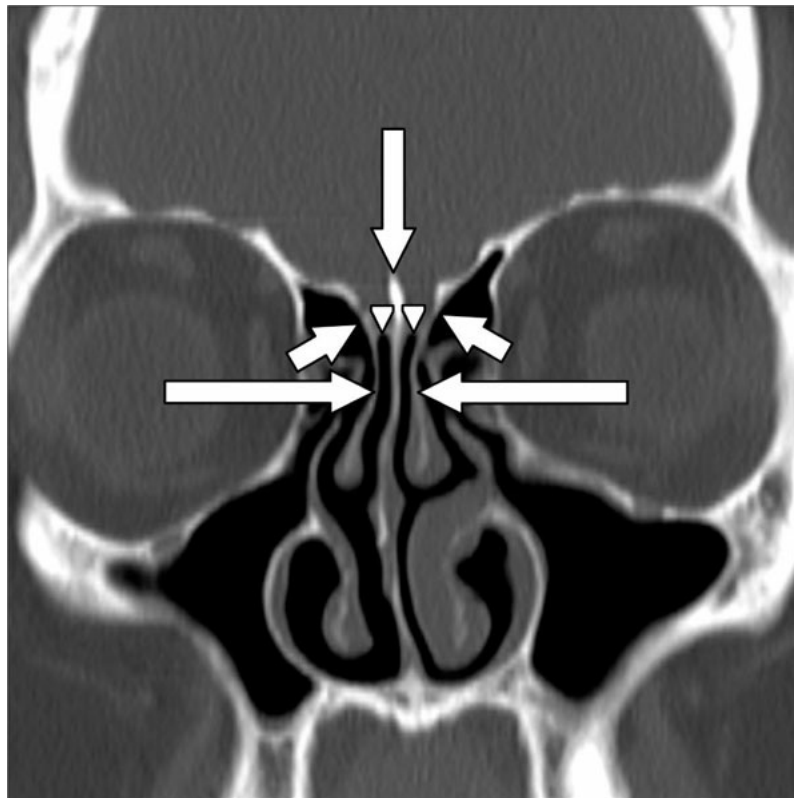
■ **FIGURE 10.3** Basal lamella and cribriform plate. Coronal CT image viewed with a bone window through the anterior skull base demonstrates the basal lamellae as cephalad extensions of the middle turbinates (*large arrows*). The basal lamellae attach to the lateral lamellae of the cribriform plate (*small arrows*). The medial lamellae (*arrowheads*) of the cribriform plate and the crista galli (*medium arrow*) are also shown.
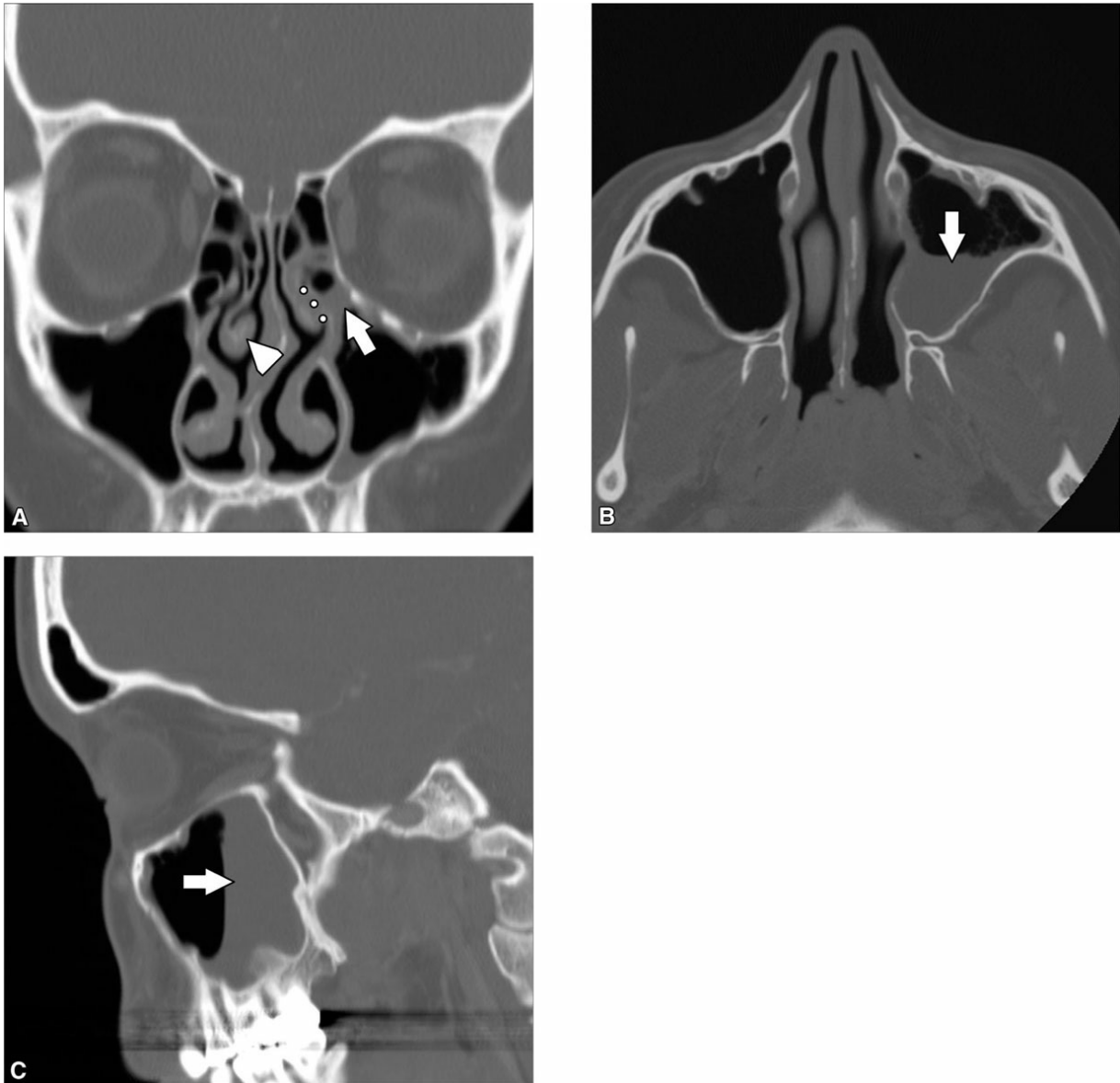
■ FIGURE 10.4 Opacified ostiomeatal complex. Coronal CT image viewed with a bone window **(A)** demonstrates opacification of the left infundibulum (*small arrow*) and left middle meatus (*dots*). A paradoxical right-middle turbinate is incidentally noted (*arrowhead*). Axial **(B)** and sagittal **(C)** CT images viewed with a bone window of the same patient demonstrate a moderate-sized air-fluid level layering dependently in the left maxillary sinus (*small arrows*).
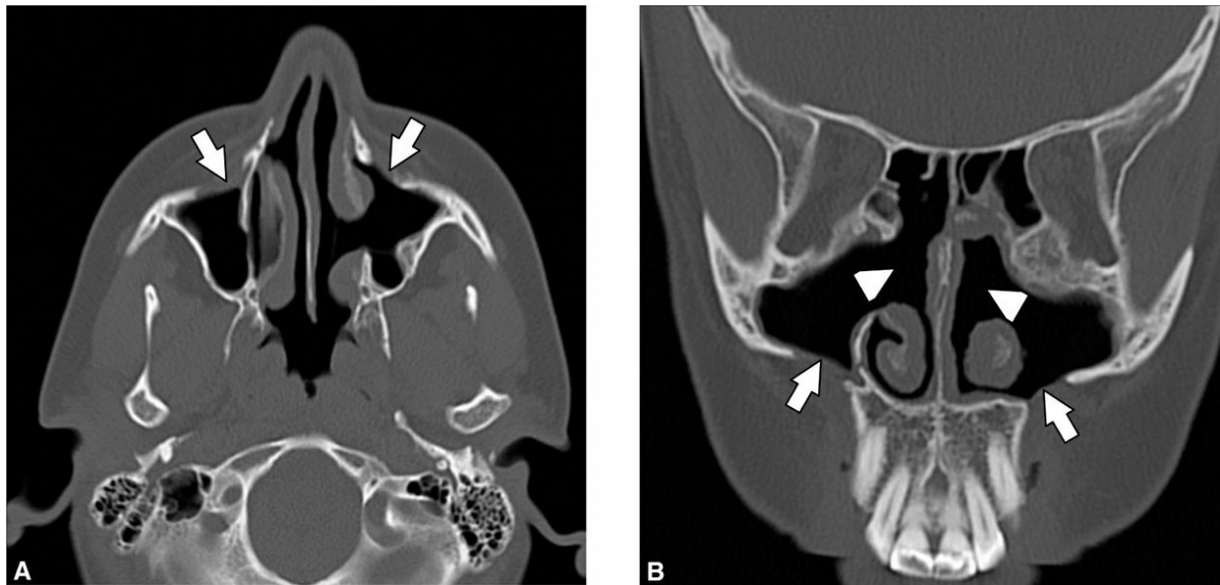
■ **FIGURE 10.5** Caldwell–Luc procedure. Axial **(A)** and coronal **(B)** CT images viewed with a bone window demonstrate surgical defects in the anterior walls of the maxillary sinuses (*small arrows*) and large maxillary antrostomies (*arrowheads*). Caldwell–Luc procedures are no longer performed to treat sinus inflammatory disease.

Extending superomedially from the maxillary sinus ostium is an aerated channel termed the *infundibulum,* which is bordered by the orbital wall laterally and by the uncinate process medially. The uncinate process is a thin osseous plate that arises as a cephalad extension from the lateral wall of the nasal cavity posterior to the nasolacrimal fossa (Fig. 10.1). Secretions passing through the infundibulum reach the hiatus semilunaris, which is a region located caudal to the ethmoid bulla (the largest anteroinferior ethmoid air cell) and immediately cephalad to the uncinate process tip (1–4). This in turn opens into the middle meatus inferiorly. Secretions from the middle meatus drain into the nasal cavity, posteriorly through the nasal choanae, and into the nasopharynx (1,2). Eventually, the secretions are swallowed.

The superior meatus is the region lateral to the superior turbinate. It receives secretions from the posterior ethmoid cells and the sphenoid sinus. The outflow tract between the sphenoid sinus and the posterior ethmoids is termed the *sphenoethmoidal recess* (Fig. 10.1). This distinct functional unit is sometimes called the *posterior ostiomeatal complex.* The inferior meatus, which resides lateral to the inferior turbinate, does not serve as a drainage passageway for sinus secretions, but rather receives tears draining from the nasolacrimal sac and duct (1,3).

The frontal sinus outflow tract is a third functional unit and comprises the

lower frontal sinus, the frontal ostium, and the frontoethmoidal (frontal) recess (6). The frontal sinus outflow tract has an hourglass configuration on sagittal reformatted images. As the frontal sinus tapers inferiorly, it forms the frontal ostium, which is the narrowest portion of this hourglass configuration (6). Just inferior to the frontal ostium is the frontoethmoidal recess, which typically drains into the anterior ethmoids and then the middle meatus via anterior ethmoid ostia. Alternatively, the frontoethmoidal recess may directly drain into the middle meatus, depending upon the configuration of the uncinate process.

Anatomic Variants

Earwaker (7) analyzed the computerized tomography (CT) scans of 800 patients who were referred for evaluation prior to FESS. He found that only 57 of these 800 patients did not have anatomic variants. Of the described 52 types of anatomic variants, 93% of the patients had one or more variants. While these variants are frequently of no clinical significance, in some circumstances they may predispose to obstruction of the normal pathways of mucus drainage, or they may increase the risk of complications associated with FESS. Therefore, familiarity with some of the more common variants is important.

Several variations in the anatomy of the nasal cavity can result in narrowing of the nasal cavity and ultimately obstruct secretions arising from the ipsilateral maxillary sinus, ethmoid air cells, and ipsilateral frontal sinus. For example, the nasal septum may be severely deviated toward one side (Fig. 10.6), narrowing the nasal cavity and compromising the middle meatus of the OMC. An osseous nasal septal spur, with or without nasal septal deviation, may similarly compromise the nasal cavity and middle meatus.
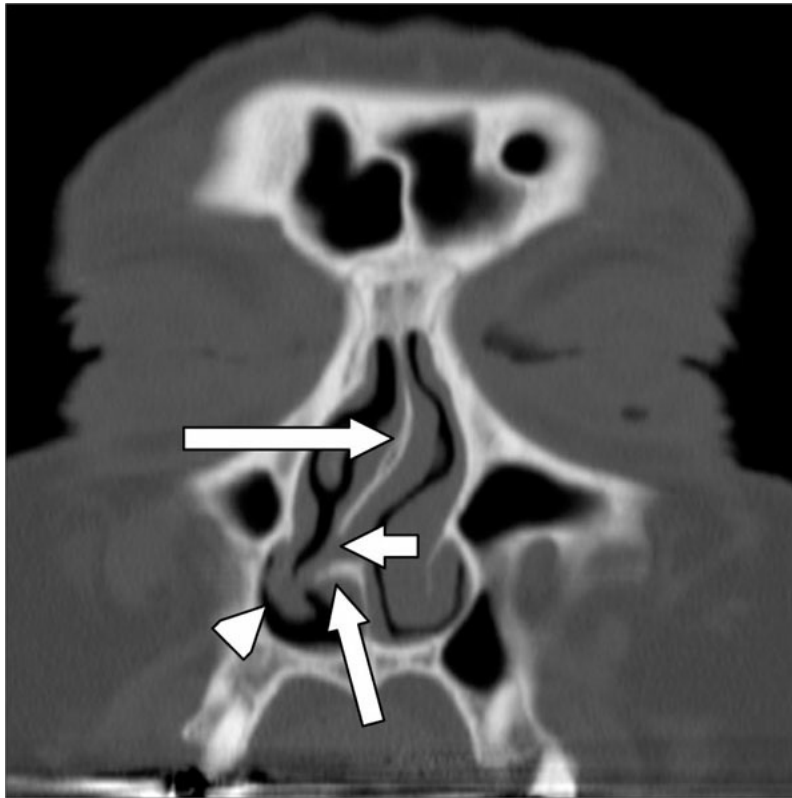
■ **FIGURE 10.6** Nasal septal deviation. Coronal CT image viewed with a bone window demonstrates marked deviation of the nasal septum, with the vomer deviated to the right (*small arrow*) and the perpendicular plate of the ethmoid (*large arrow*) deviated to the left. A superimposed spur (*medium arrow*) is associated with deformity of the right inferior turbinate (*arrowhead*).

A concha bullosa (Figs. 10.7 and 10.21) is an aerated turbinate head, most commonly associated with the middle turbinate, although aeration can also be seen in the superior and inferior turbinate heads (3,8). Various studies use different degrees of pneumatization to define a concha bullosa; consequently, the reported prevalence has a wide range from 22% to 55% (3,8). There is a strong relationship between the presence of a concha bullosa and contralateral nasal septal deviation, although Stallman et al. (9) found no significant increase in paranasal sinus disease associated with a concha bullosa. Concha bullosa are lined by secretory mucoperiosteum and are therefore prone to the same disease processes that can affect the paranasal sinuses (10).

Normally, the middle turbinate necks are bowed convex medially and their heads project laterally. A paradoxical middle turbinate (Figs. 10.4 and 10.8) refers to a middle turbinate in which its neck is bowed convex laterally and its head projects medially. This is a common variant and is most often an incidental finding. Rarely, the middle meatus may be narrowed by a paradoxical middle turbinate and can predispose to sinus obstruction when associated with mucosal

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inflammation or edema. Occasionally, paradoxical middle turbinates may make surgical access to the OMC difficult (3,8).
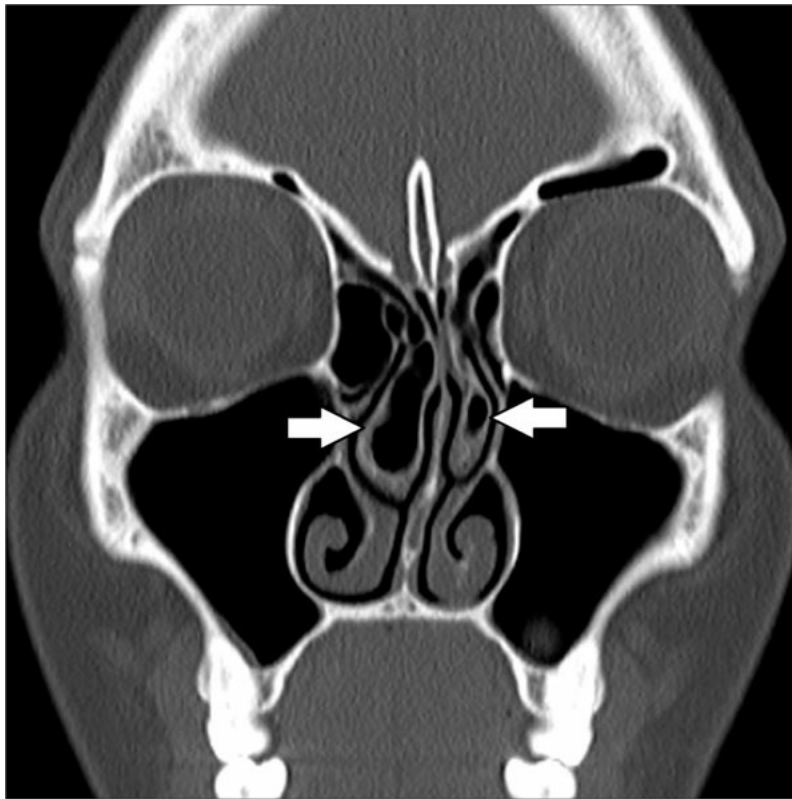
■ FIGURE 10.7 Concha bullosa. Coronal CT image viewed with a bone window through the mid-nasal cavity demonstrates bilateral concha bullosa involving the middle turbinates, right larger than left (*arrows*).

The uncinate process can have varying appearances. The orientation of the uncinate process may be vertical, horizontal (particularly in conjunction with a large ethmoid bulla), or anywhere in between (3,8). The uncinate process may also be pneumatized and expanded, potentially compromising the infundibulum. Moreover, instead of terminating as a free sharp tip at its cephalad margin, an uncinated process can attach to several sites within the paranasal sinuses. For example, the uncinate process tip may extend directly cephalad and attach to the ipsilateral fovea ethmoidalis (roof of the ethmoid), or may extend medially and attach to the neck of the middle turbinate. If the tip of the uncinate process projects superolaterally and attaches to the medial wall of the orbit, it forms a blind-ending air cell along its superior margin, which directly communicates with the maxillary sinus. This variant is termed a recessus terminalis. These various attachment sites of the uncinate process will affect the direction of outflow for the ipsilateral frontal sinus and ethmoid air cells (6). If the uncinate process attaches to the fovea ethmoidalis or neck of the middle turbinate, then flow of secretions from the frontal sinus and ethmoid air cells will be directed

toward the infundibulum. However, if the uncinate process terminates as a recessus terminalis, then the flow of secretions will be directed directly into the middle meatus, thereby bypassing the infundibulum.
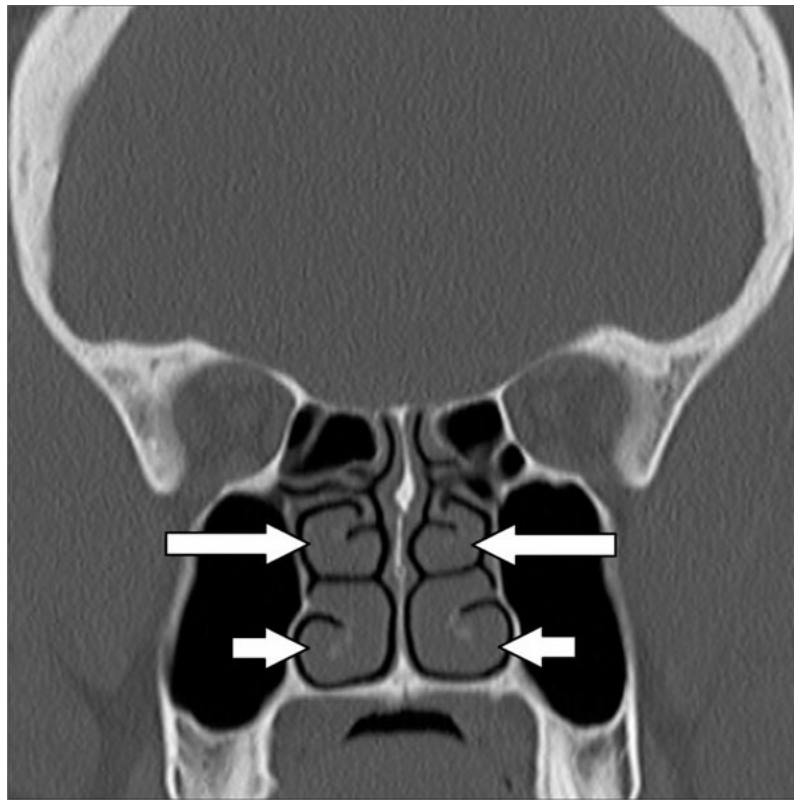
■ **FIGURE 10.8** Paradoxical middle turbinates. Coronal CT image viewed with a bone window demonstrates bilateral paradoxical middle turbinates (*medium arrows*). The heads of these middle turbinates curve inward rather than outward, as opposed to the normal configuration of the inferior turbinate heads (*small arrows*).

A deviated nasal septum and an associated osseous spur often contact and are associated with deformity of the adjacent turbinates. Since the nose and paranasal sinuses are innervated by the first and second divisions of the trigeminal nerve (11), the potential exists for "contact point" headaches. These contact point headaches are believed to represent referred headaches from stimulation of the trigeminal nerve and can improve following surgical removal of the spur and a septoplasty (12,13). However, the presence or severity of a contact point between a septal deviation/spur and a turbinate is not a primary indication for surgery (12). Furthermore, careful history, physical exam, and other potential causes for the patient's headaches should be considered prior to surgery.

Many common variants arise from the ethmoid air cells and extend into the

adjacent sinuses or outflow tracts. These are collectively termed *extramural ethmoid air cells* (1,3,6,8). One of the more common variants is the Haller cell (Figs. 10.1 and 10.9). The Haller cell is an air cell that lies within the superomedial maxillary antrum and adjacent to the inferior medial margin of the orbit. A large Haller cell may narrow the primary maxillary sinus ostium or the infundibulum, depending upon its position. Agger nasi cells (Fig. 10.10) are extremely common, and when present, represent the most anterior of all the ethmoidal air cells. They reside within, or adjacent to, the lacrimal bones and just ventral to the nasolacrimal canal. When large or strategically located, they may anatomically narrow the frontoethmoidal recess (3,6). Agger nasi cells are important surgical landmarks to identify the position of the frontoethmoidal recess. A frontal bulla (Fig. 10.11) is an ethmoid air cell that extends along the back wall of the frontoethmoidal recess and into the frontal sinus, occasionally resulting in obstruction of the frontal sinus and/or frontoethmoidal recess (6,14). Onodi cells (Fig. 10.12) are posterior ethmoid air cells that share a common wall with the optic canal and typically reside cephalad to the sphenoid sinus. The significance of the Onodi cell relative to surgery is discussed in the next section of this chapter.
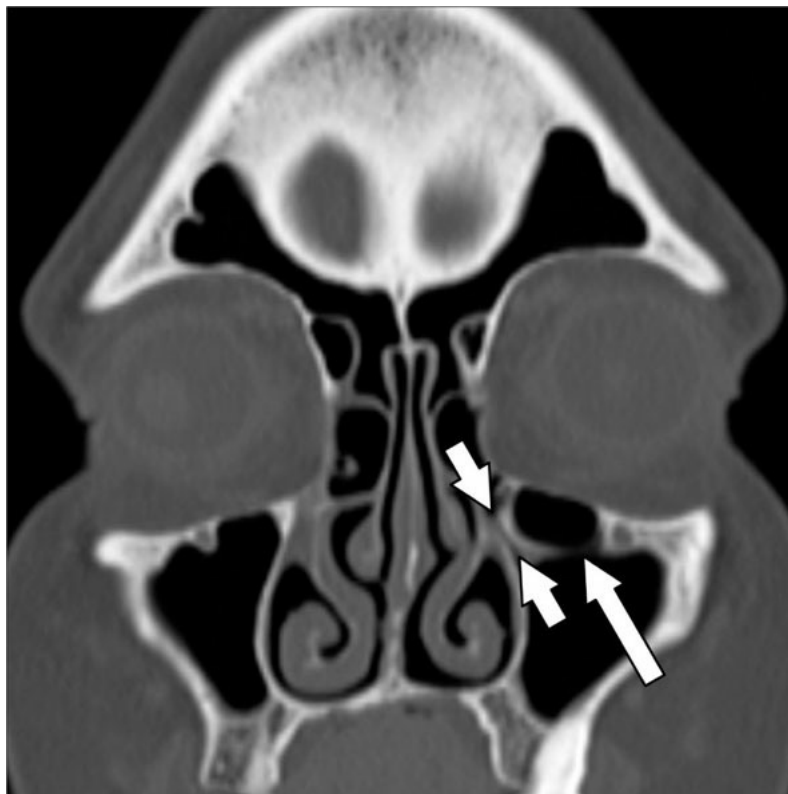
■ **FIGURE 10.9** Haller cell. Coronal CT image viewed with a bone window demonstrates a moderate-sized Haller cell (*medium arrow*) that forms the lateral margin of the left infundibulum (*small arrows*). Haller cells can result in

narrowing or obstruction of an infundibulum. In this case, the left infundibulum is narrowed by the Haller cell and opacified because of superimposed mucosal thickening.
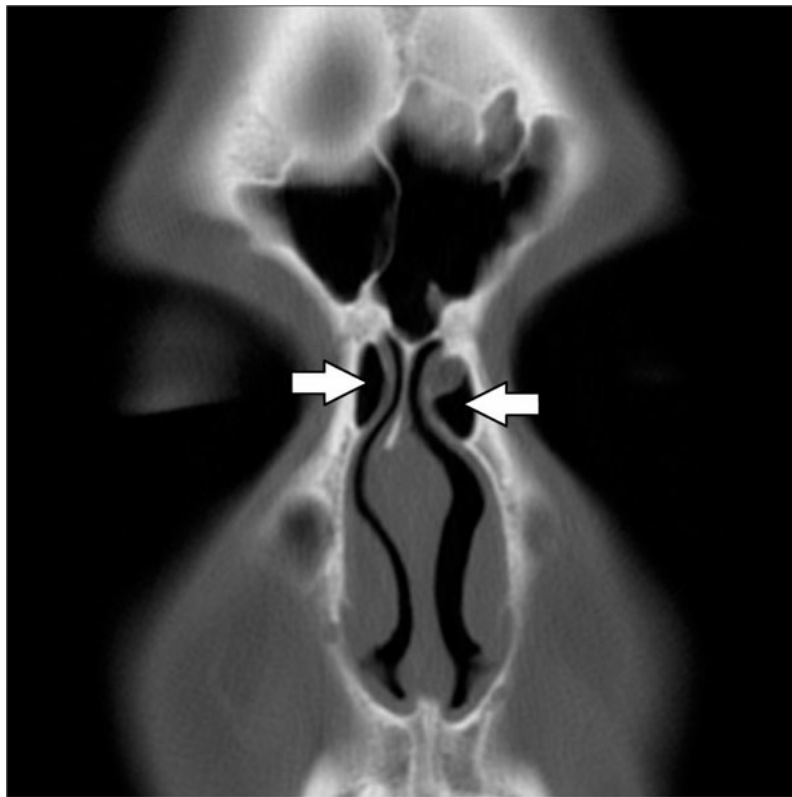
■ **FIGURE 10.10** Agger Nasi cells. Coronal CT image viewed with a bone window demonstrates paired Agger Nasi cells (*arrows*), with the one on the left containing mild mucosal thickening.
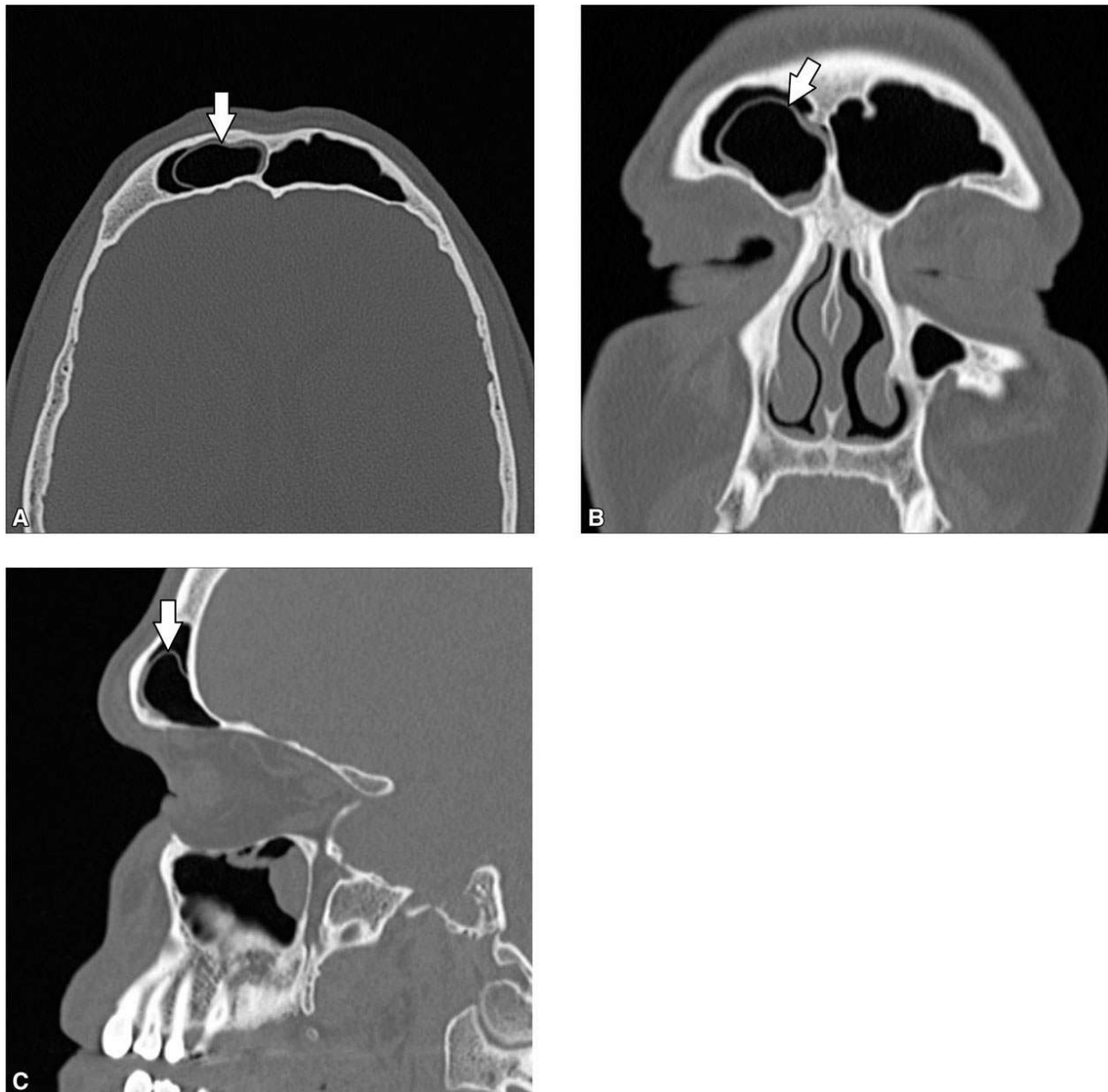
FIGURE 10.11 Frontal bulla. Axial CT image viewed with a bone window **(A)** demonstrates an additional air cell within the right frontal sinus (*arrow*), consistent with a frontal bulla. A frontal bulla can result in obstruction of the ipsilateral frontal sinus by obstruction the frontoethmoidal recess, although the frontal sinus in this patient is relatively clear at the time of scanning. Coronal **(B)** and sagittal **(C)** CT images viewed with a bone window also demonstrate the frontal bulla (*arrows*).

Complications of Functional Endoscopic Sinus Surgery—Anatomic Considerations

The anatomy of the nasal cavity and ethmoid labyrinth is complex and variable. Endoscopy provides a two-dimensional view of three-dimensional anatomy. Conventional cross-sectional imaging, and more recently intraoperative framed

and frameless stereotactic guided imaging techniques, can help avoid complications from endoscopic sinus surgery.

When surgical complications do occur, CT and magnetic resonance imaging (MRI) are essential for evaluation. A common site prone to complications is the lamina papyracea (the medial orbital wall), which may be breached during ethmoid surgery. In addition, the surgeon should be aware of any preexisting lamina papyracea deformities to avoid inadvertent breach of the orbit.

■ **FIGURE 10.12** Onodi cell. Axial **(A)** and coronal **(B)** CT images viewed with a bone window demonstrate a posterior most left ethmoid air cell (Onodi cell) (*medium arrows*) forming a margin with the left optic canal (*arrowheads*). The Onodi cell extends into and pneumatizes the left anterior clinoid process (*small arrow*). The typical location for an Onodi cell is superior to the sphenoid sinus (*dots*), as the coronal image demonstrates.

Variations in the degree of pneumatization of the sphenoid sinus can also result in surgical mishap. Pneumatization of the sphenoid sinus can extend into the anterior clinoid processes. The anterior clinoid process normally forms a portion of the optic canal lateral wall. If the surgeon is unaware of its presence, surgery through a pneumatized anterior clinoid process can result in a larger than intended osteotomy and subsequent injury to the optic nerve. As discussed earlier, Onodi cells (Fig. 10.12) are posterior ethmoid air cells that share a common wall with the optic canal. If a surgeon is unaware of the presence of an Onodi cell, the surgeon could inadvertently breach the optic canal and damage the optic nerve. The presence and exact location of an Onodi cell can be defined only prior to surgery with cross-sectional imaging, ideally with CT. The internal carotid artery resides lateral to the sphenoid sinus wall and, if medially

positioned, may bulge into the sphenoid sinus lumen and be predisposed to injury during sinus surgery; this may lead to serious hemorrhage or pseudoaneurysm formation (Fig. 10.13). Often, the sphenoid septum attaches to one of the carotid canals. If this is present, the potential exists for a fracture to the carotid canal during resection of the sphenoid septum.

The roof of the ethmoid air cells is formed by the frontal bone (15). An asymmetric, low-lying ethmoid roof increases the risk of inadvertent breech by the unsuspecting surgeon and may result in herniation of the brain and/or meninges as well as a cerebrospinal fluid (CSF) leak. The cribriform plate, which resides at the midline between the roofs of the ethmoids, contains medial and lateral lamellae (Fig. 10.3). The lateral lamella is an extremely thin osseous structure and is a point of structural weakness along the anterior skull base (3,15,16). Moreover, the anterior ethmoidal artery enters the intracranial compartment through the lateral lamella of the cribriform plate via the anterior ethmoidal sulcus (or groove). Therefore, if the lateral lamella is breached, the anterior ethmoidal artery may be damaged and result in intracranial hemorrhage (16,17) or arteriovenous fistula formation. Other potential sites of injury to the anterior ethmoidal artery require further understanding of its anatomic course. The anterior ethmoidal artery arises from the ophthalmic artery within the orbit. The artery ultimately exits medially into the anterior ethmoidal foramen and then into a pyramidal-shaped notch located along the superomedial margin of the orbit termed the anterior ethmoidal canal (16). The location of the anterior ethmoidal canal is vitally important to the surgeon; it serves as an anatomic landmark and is avoided during routine sinus surgery in order to prevent injury to the artery. In addition, as the artery exits this foramen, occasionally it may traverse the superior ethmoid air cells, within or without an osseous canal, prior to extending intracranially. If the anterior ethmoidal artery is injured in this region, then the artery can retract into the orbit and result in uncontrolled intraorbital hemorrhage, increased intraorbital pressure, and possibly blindness from retinal artery occlusion (17). Operative injuries to the orbital walls, cribriform plate, and ethmoid roofs are typically best identified on coronal CT (Fig. 10.13), but the possible complications of cerebritis, meningitis, cephalocele, empyema, or abscess are best demonstrated on contrast-enhanced MRI.

As discussed earlier, a CSF leak is another known complication of FESS and is usually the result of injury to the roof of ethmoids or cribriform plate. Patients may present with CSF rhinorrhea, recurrent meningitis, and a meningoencephalocele (18,19). Symptoms may occur immediately or be delayed

several years after the operative procedure or trauma (20). A radionuclide cisternogram can be performed to confirm the presence of a leak, but this test provides only limited anatomic information concerning the exact location of the leak. A noncontrast CT can be performed in the axial and coronal planes to localize a fracture and has been shown to demonstrate the site of a CSF fistula 71% of the time (21). A CT cisternogram is a procedure whereby contrast is placed into the subarachnoid space (via a lumbar puncture) and a CT is performed with direct coronal images (Fig. 10.14). The coronal images are ideally obtained with the patient placed prone to promote leakage of contrast through the defect. The reported sensitivity of CT cisternography to detect CSF leaks (of all causes) is 36% to 81%. Although CT cisternography can aid in anatomical localization of the site of a leak, the sensitivity is diminished if the patient is not actively leaking CSF at the time of the exam (20,22). If a patient is leaking CSF, a β_2-transferrin can be sent for laboratory analysis to verify that there is a CSF leak. Some authors advocate the use of MRI with or without intrathecal gadolinium contrast to localize the site of a CSF leak (20,21) (Fig. 10.15). T2-weighted images provide excellent contrast between the CSF and bone–air interface. Continuity of elevated T2 signal CSF from the intracranial subarachnoid space through an osseous defect into extracranial sites can sometimes be identified (20). However, a potential drawback to MRI cisternography is that the CSF and gadolinium may be obscured by fluid (on T2-weighted imaging) and enhancing mucosal thickening (on contrast-enhanced T1-weighted imaging) in the sinuses, respectively. Additionally, CT provides superior bone detail compared to MRI (20,22). Currently, most practitioners perform either a noncontrast CT, with or without a β_2-transferrin assay, or CT cisternography.
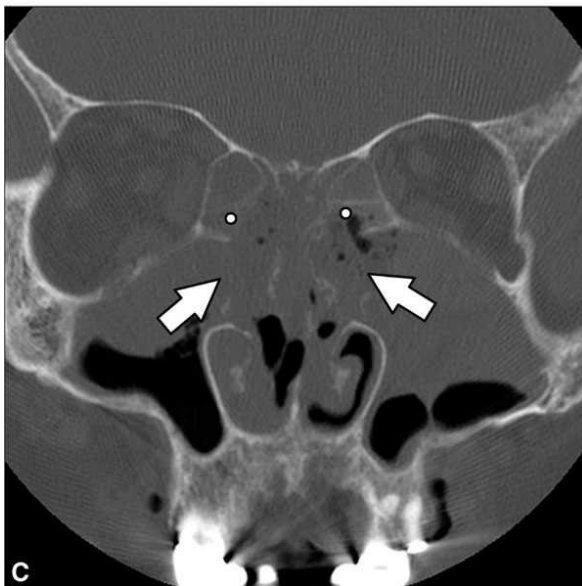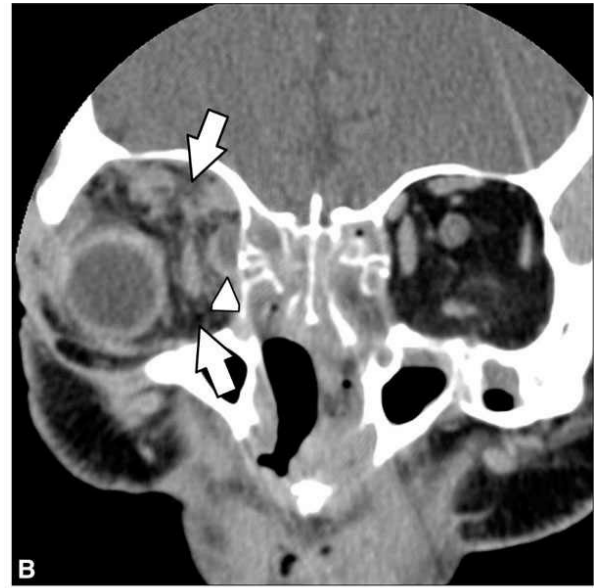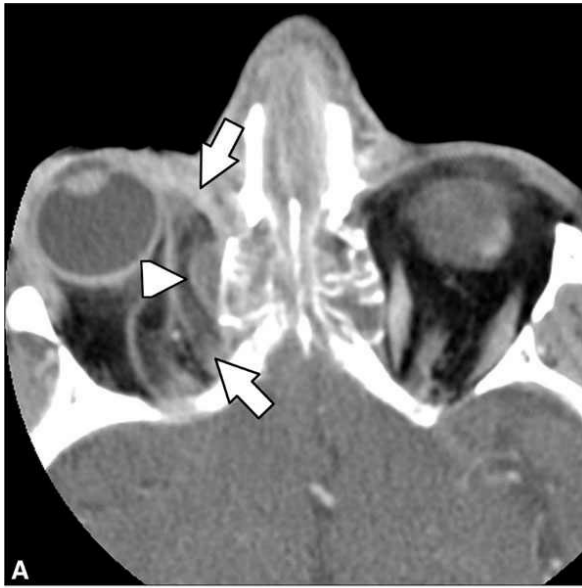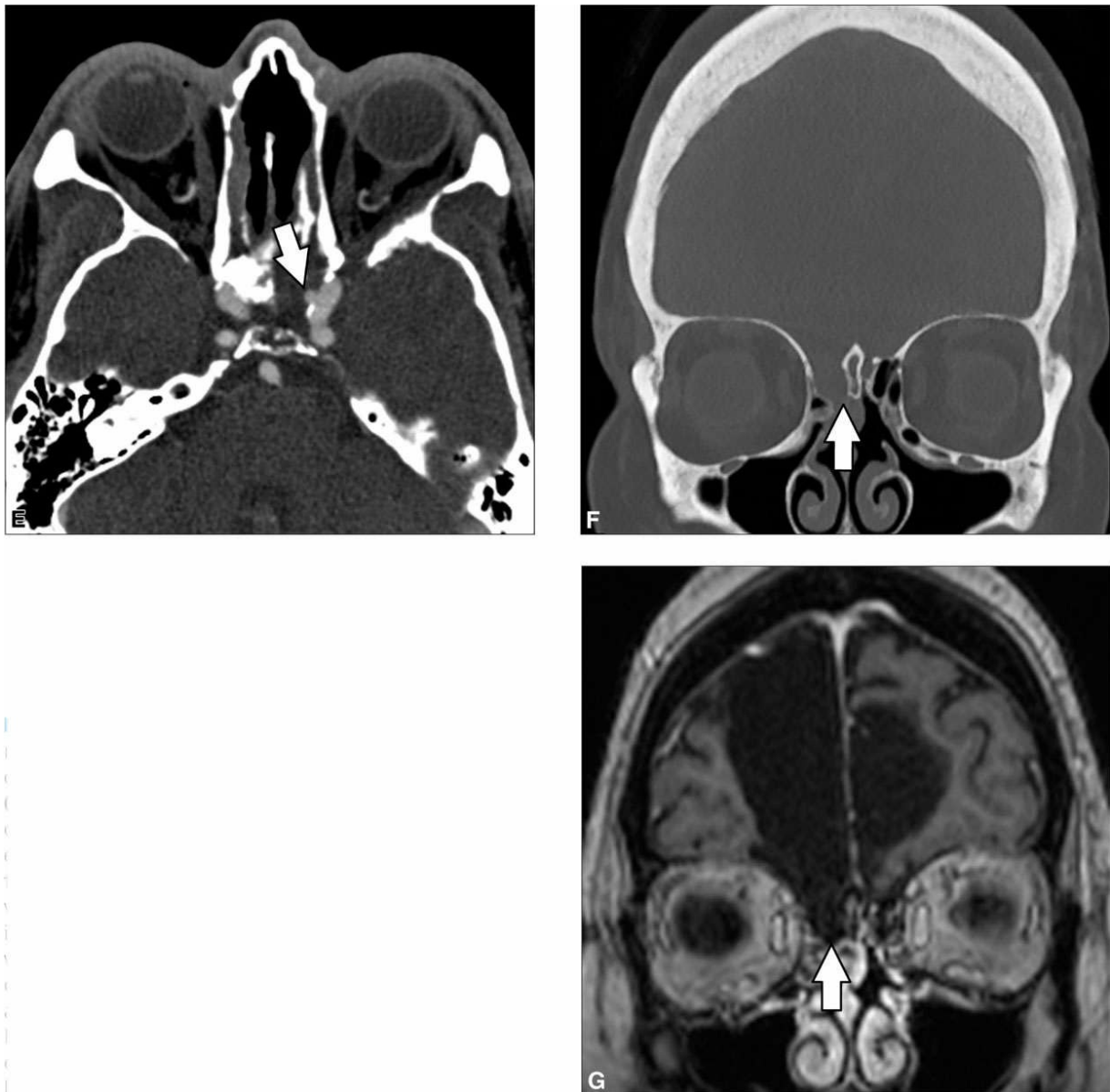
■ FIGURE 10.13 Surgical complications. Post-contrast axial **(A)** and coronal **(B)** CT images viewed with a soft tissue window from a patient who developed right eye pain and proptosis 1 week after sinus surgery. Diffuse inflammation and enhancement in the right orbit (*small arrows*) are compatible with infection. A peripherally enhancing fluid collection in the medial right orbit (*arrowheads*) was found to be an subperiosteal abscess at the time of surgical drainage. A coronal CT image **(C)** viewed with a bone window from the same patient demonstrates the surgical changes in the sinuses, including bilateral maxillary antrostomies and uncinectomies (*small arrows*) as well as partial ethmoidectomies (*dots*). A post-contrast axial CT image **(D)** viewed with a soft tissue window from a different patient who presented with epistaxis. This patient had multiple prior sinus surgeries as well as endoscopic resection of a pituitary tumor.

A focus of contrast in the left nasal cavity (*small arrow*) is compatible with a pseudoaneurysm of the anterior ethmoidal artery. A post-contrast axial CT image **(E)** viewed with a soft tissue window from the same patient, obtained after treatment of the anterior ethmoidal pseudoaneurysm, shows interval development of a vascular outpouching from the left internal carotid artery (*small arrow*), compatible with an internal carotid artery pseudoaneurysm. Coronal CT image **(F)** viewed with a bone window from a different patient who developed a cerebrospinal fluid leak after sinus surgery demonstrates a bony defect in the right fovea ethmoidalis and cribriform plate (*small arrow*). Coronal post-contrast MP RAGE T1 MR image **(G)** from the same patient demonstrates extension of meninges and cerebrospinal fluid through the bony defect (*small arrow*), compatible with a meningocele.
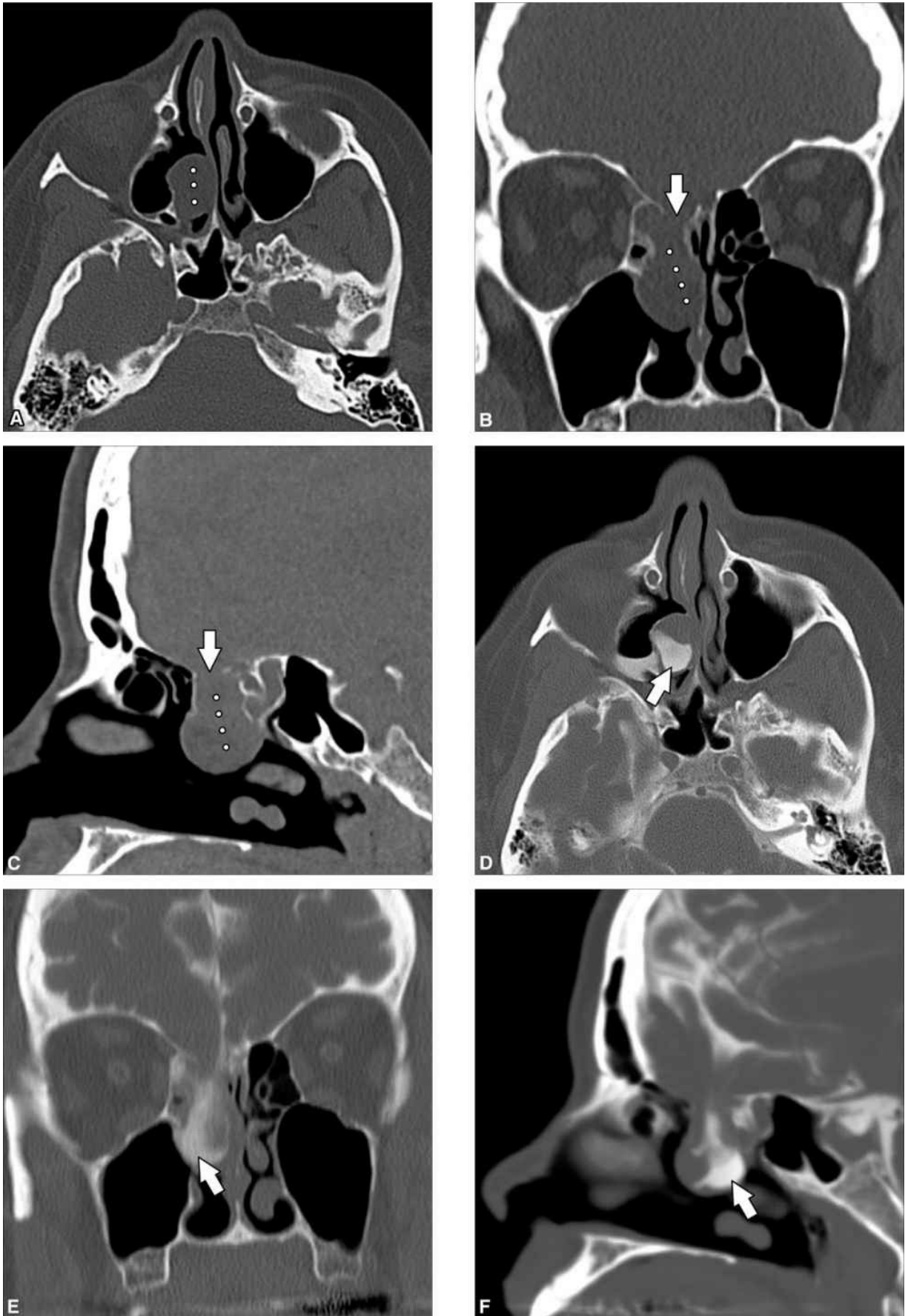
■ **FIGURE 10.14** Encephalocele. Axial **(A)**, coronal **(B)**, and sagittal **(C)**

noncontrast CT images through the sinuses viewed with a bone window demonstrate a relatively large osseous defect involving the roof of the right ethmoid, including the right lateral lamella (*arrows*). A nonspecific opacity is present in the right posterior ethmoid air cells, suggestive of a cephalocele (*dots*), given the osseous defect involving the overlying right ethmoid roof. Axial **(D)**, coronal **(E)**, and sagittal **(F)** CT images through the sinuses, viewed with a bone window, following intrathecal administration of contrast demonstrate contrast extending into the lesion within the right posterior ethmoids. The partial opacification of the lesion with contrast (*arrows*) confirm that the lesion is partially cerebrospinal fluid and partially brain tissue. This is consistent with an encephalocele.
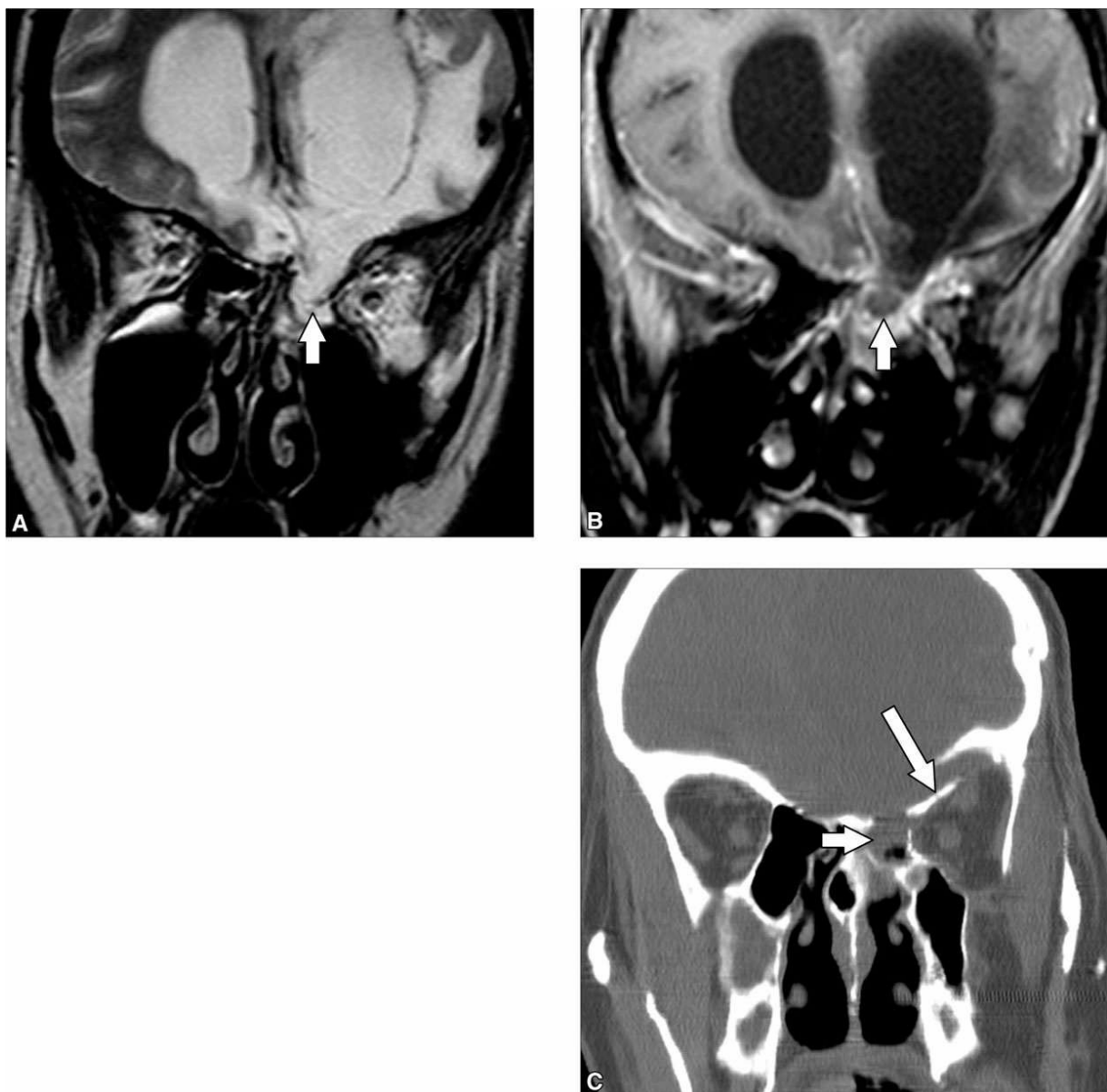
■ **FIGURE 10.15** Ethmoidal meningocele following trauma. A coronal T2-weighted MR image **(A)** demonstrates a defect at the roof of the left ethmoid air

cells with meninges and cerebrospinal fluid extending through the defect (*arrow*), consistent with a meningocele. A coronal T1 post-contrast fat suppressed MR image **(B)** and a coronal CT image viewed with a bone window **(C)** demonstrate the same finding (*small arrows*). A fracture to the roof of the left orbit is also seen on the CT image (*medium arrow*).

Empty nose syndrome (Fig. 10.16) refers to the sensation of nasal congestion that occurs from an atrophic rhinitis or following advanced resection of the nasal turbinates (18,23). The function of the turbinates is to filtrate, warm, and humidify inhaled air. Absence of the nasal turbinates following surgery results in alteration of airflow and decreased nasal sensation. Despite the presence of a widely patent nasal cavity, the patient paradoxically experiences a congested nasal sensation (18,23). Although the empty nose syndrome is considered rare (18,23), this entity is likely directly proportional to the extent of the turbinate resection performed during surgery.

■ IMAGING TECHNIQUE

Full radiographic imaging of the sinuses is usually reserved for those patients with clinical signs and symptoms of rhinosinusitis who have failed standard medical treatment, such as patients with chronic rhinosinusitis or those who have recurrent episodes of rhinosinusitis and are potential surgical candidates. Depending on the modality, anatomic causes and underlying disease processes can be visualized, and the feasibility as well as the risk of surgery can be evaluated. Additionally, a patient with a suspected complication of rhinosinusitis or a presumed surgical complication should be imaged.
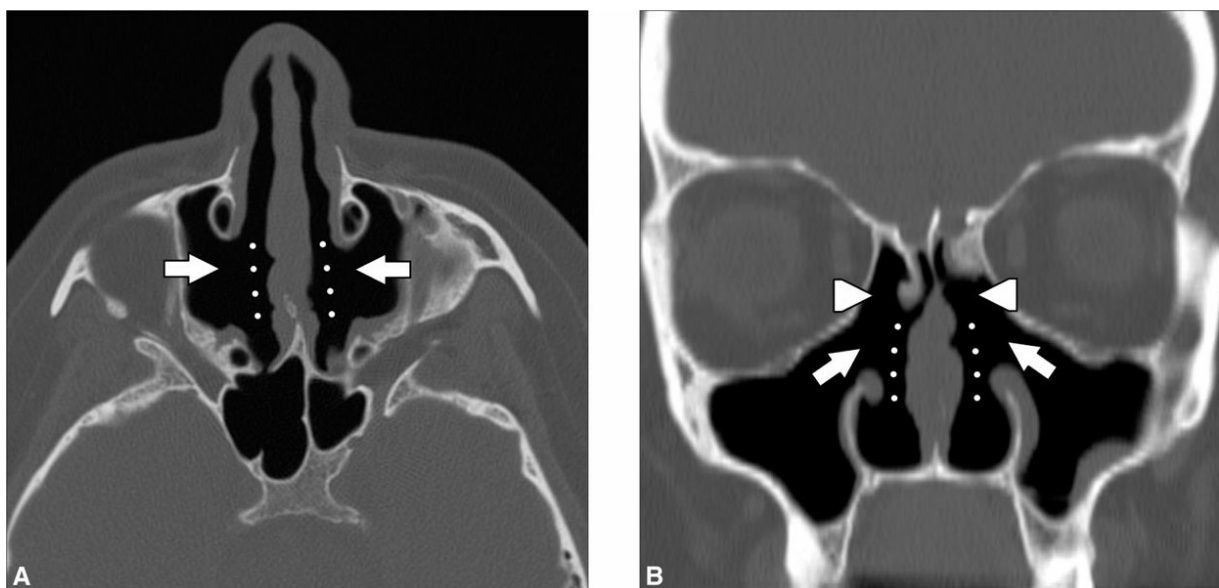
■ **FIGURE 10.16** Empty nose syndrome. Axial **(A)** and coronal **(B)** CT images

viewed with a bone window demonstrate absent turbinates (*dots*), uncinectomies with antrostosmies (*small arrows*), and ethmoidectomies (*arrowheads*). This patient had symptoms of chronic rhinosinusitis. Turbinates humidify inhaled air. The lack of the turbinates results in a congested sensation for the patient.

Standard radiography, while being fast and inexpensive, is of marginal benefit to evaluate the paranasal sinuses, particularly relative to cross-sectional imaging modalities (1,18,24). Areas that may be evaluated by standard radiography include the lower third of the nasal cavity and the maxillary, frontal, and sphenoid sinuses as well as the posterior ethmoid air cells. The anterior ethmoid cells, the upper two-thirds of the nasal cavity, and the outflow tracts are often obscured by overlapping structures.

CT is the imaging modality of choice for routine evaluation of the paranasal sinuses. When performed for preoperative evaluation of fixed sinus obstructive disease, some clinicians recommend pre-imaging patient preparation consisting of a course of antibiotics to eliminate any acute or transient mucoperiosteal disease. This is followed by sympathomimetic spray just prior to the scan to minimize reversible congestion and mucus (3). In theory, this will allow for optimal delineation of the chronic nonreversible sinus disease that should be the target of operative intervention. This also optimally serves to evaluate the anatomy and to determine if there are any anatomic causes of obstruction resulting in sinus disease.

With the advent of helical CT scanning, several of the difficulties with patient positioning have been eliminated, and there are opportunities for reducing radiation dose and examination time. This technology allows for rapid acquisition of volumetric data that can be subsequently reformatted at narrow increments in any plane chosen.

Coronal and axial imaging is preferred prior to FESS (3). Coronal plane images optimally visualize the OMC and demonstrate anatomy that corresponds to the surgeon's orientation during endoscopy. Sagittal reformatted imaging may also be obtained, and is perhaps most useful to evaluate the frontoethmoidal recesses. With current CT scanners, reformatted images can easily be performed. Images are obtained and displayed at both wide "bone" windows and narrow "soft tissue" windows. One should remember that an air–fluid level will be best identified on direct axial imaging but will frequently be occult on coronal reformatted imaging. This is because when the patient is imaged by CT, they are placed in a supine position and scanned in the axial plane. An air–fluid level in this position will lie dependently along the back wall of the sinus and orthogonal

to the axial plane of imaging. This results in an air–fluid level that is easily identified. However, when this same data set is reconstructed in the coronal plane, the air–fluid level will lie in the same plane as the coronal images, and it will appear as a homogeneous sinus opacification, rather than an air–fluid level (Fig. 10.17).
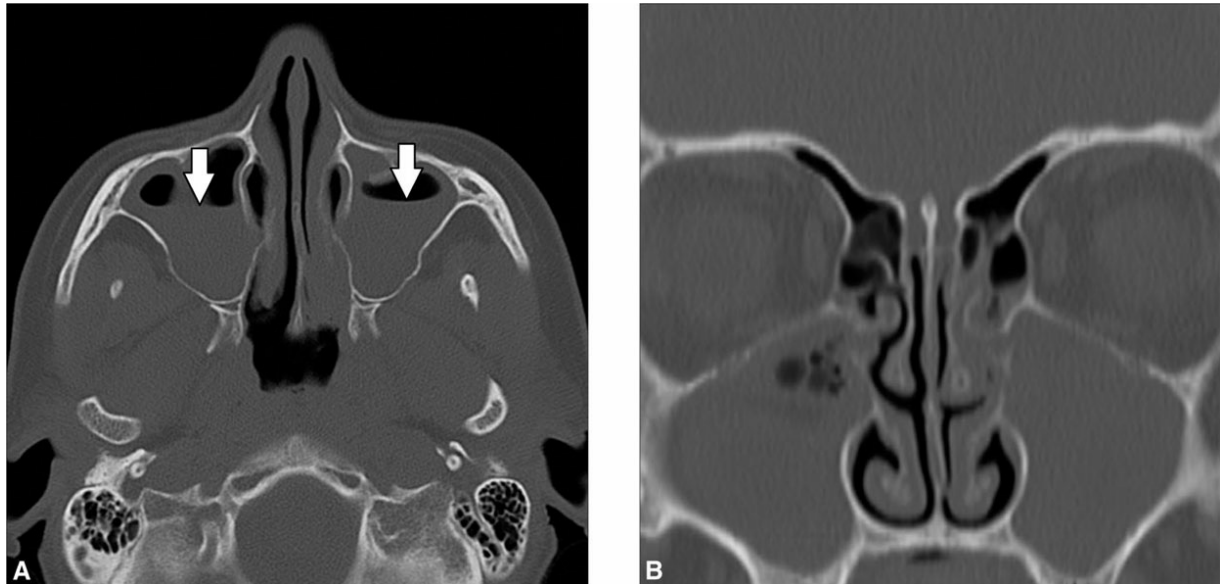
■ **FIGURE 10.17** Acute rhinosinusitis. Axial CT image viewed with a bone window **(A)** demonstrates air-fluid levels (*arrows*) layering dependently in the maxillary sinuses. In the appropriate clinical setting, this would be consistent with acute rhinosinusitis. Coronal CT image viewed with a bone window through the posterior aspect of the maxillary antra in the same patient **(B)** gives the false impression that the maxillary antra are nearly completely opacified. The axial image reveals the true configuration of the fluid at the time of scanning because the patient lies supine during the image acquisition.

An advantage of MRI over CT scans is the lack of ionizing radiation and improved soft tissue contrast. In addition, the extensive artifact from dental hardware that can occur with CT is usually less problematic with MRI. It is clear that the bone detail necessary for evaluating the paranasal sinuses is superior on CT, whereas intraorbital and intracranial contents are better demonstrated on MRI. Consequently, MRI is the technique of choice for evaluating the complications of rhinosinusitis, primary sinus neoplasms, the spread of neoplastic processes, and postoperative complications. MRI is not the primary modality for evaluating uncomplicated sinus inflammatory disease, which is the role of CT (1,18,25).

■ RHINOSINUSITIS

Acute Rhinosinusitis

Rhinosinusitis, rather than simply sinusitis, is the preferred term for describing sinus inflammatory disease, since sinusitis is often preceded by rhinitis and rarely occurs without concomitant nasal inflammation (26). Acute rhinosinusitis often occurs following an upper respiratory tract infection. The respiratory infection causes mucoperiosteal congestion. At the level of the ostia, there is apposition of mucosal surfaces with obstruction of normal mucociliary clearance, resulting in retention of secretions and stasis. Transient ostial obstruction may lead to sterile fluid accumulation. This obstruction results in a decrease in oxygen tension and an increase in carbon dioxide tension within the sinus; in combination with stagnant fluid, this environment provides an excellent medium for bacterial growth (27). Clinically, rhinosinusitis may be classified as acute, recurrent acute, subacute, and chronic (28,29). These clinical categories do not have well-defined imaging correlates. Bhattacharyya et al. (30) examined the relationship of patient symptoms and CT findings in 221 subjects. These patients responded to a clinical questionnaire that assessed the severity of their symptoms prior to undergoing CT. Thirty-four percent of these patients had a normal CT scan. There was no significant correlation between the subset of patients with "positive" and "very positive" CT findings and the severity of their symptoms. Furthermore, the subgroup of patients reporting facial pain as their primary symptom had overall less impressive imaging findings than patients without facial pain.

Most patients experience a normal cyclic congestion of the mucoperiosteum lining the nasal turbinates, nasal septum, and ethmoid air cells, a process that is termed the normal nasal cycle (Fig. 10.18) (31). Consequently, mild ethmoid air cell mucoperiosteal thickening may not represent an infectious process but rather transient congestion (28). It is not surprising that a prospective study performed by Rak et al. (32) revealed that 69% of a group of patients undergoing a brain MRI for unrelated reasons demonstrated minimal (1 to 2 mm) ethmoid mucosal thickening. Sixty-three percent of these patients did not report any symptoms of rhinosinusitis. In fact, only when the mucosal thickening was 4 mm or greater was there a significant correlation with rhinosinusitis symptoms.
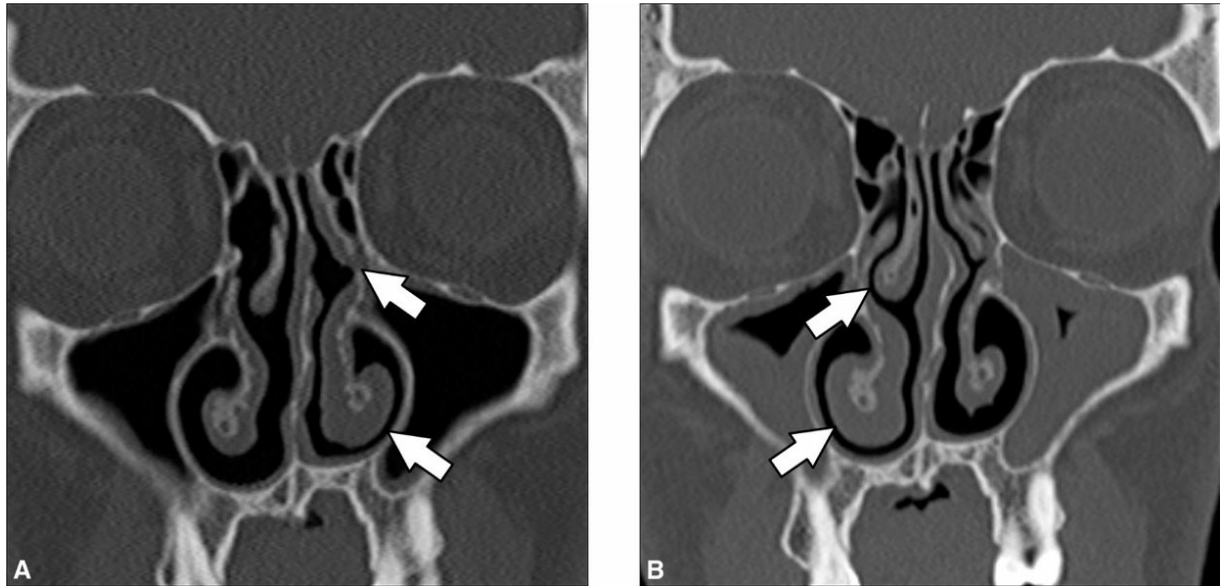
■ **FIGURE 10.18** Nasal cycle. Two coronal CT images from the same patient viewed with a bone window **(A, B)** demonstrate changes in the sizes of the nasal turbinates related to the nasal cycle. In the first image **(A)**, there is congestion of the left nasal turbinates (*arrows*). In the second image, taken months later **(B)**, there is congestion of the right nasal turbinates (*arrows*). This is the normal cyclic pattern of congestion of the turbinates.

The best imaging correlate for acute rhinosinusitis is an air–fluid level (Fig. 10.17), although fluid may accumulate without infection. Acute infection is a clinical diagnosis and imaging can support this impression (24,28). Consequently, sinus images may be interpreted descriptively, without necessarily drawing conclusions regarding the patient's clinical status.

The location of mucoperiosteal thickening is also important. For example, a patient with a relatively mild degree of mucosal thickening that opacifies the infundibulum is more likely to suffer from obstructive rhinosinusitis than a patient with mild mucosal thickening involving the inferior aspect of the maxillary antrum.

Chronic Rhinosinusitis

Chronic rhinosinusitis (CRS) may be difficult to define on a single imaging study. CRS is often associated with reactive bony sclerosis and thickening of the sinus walls (osteitis) (Fig. 10.19). This is the single best radiographic sign for CRS. In addition, if there are a series of exams demonstrating persistent mucoperiosteal thickening in a symptomatic patient, then the diagnosis of CRS is likely.

On CT scans, chronic inspissated secretions will appear as focal areas of high

attenuation, often with more peripheral low attenuation from edematous mucoperiosteum. This hyperdense appearance can also be seen with polyposis, fungal colonization, and fungal rhinosinusitis (Fig. 10.24) (24,28,29). The MRI appearance of the soft tissue contents within the sinus cavity is variable and is dependent on the proportion of water and protein contents within the secretions. Normal sinus secretions are comprised of 95% water and 5% solid materials. On MRI, the appearance of normal secretions reflects water content and is characterized as isointense or hypointense signal on T1-weighted images and hyperintense signal on T2-weighted images. With chronic obstruction, there is continuous secretory activity and also resorption of water. In addition, there are mucosal changes resulting in an increased number of glycomucoprotein-producing goblet cells. As a result, the overall water content of the secretions decreases and the protein concentration as well as viscosity increases. Initially, these changes are reflected by shortening of the T1 relaxation time and secretions are hyperintense on T1-weighted imaging. T2 relaxation time is noticeably unaffected until the protein concentration is greater than 25%. At this protein concentration, there is cross-linking of the protein molecules, which increases the viscosity of the secretions. This diminishes macromolecular motion, which further decreases the T2 relaxation time, resulting in decreased T2 signal intensity. Eventually, as the secretions become completely desiccated, there is elimination of free water and marked hypointensity on both T1- and T2-weighted sequences. As a result, the sinus disease may appear as a signal "void" on T1- and T2-weighted imaging. Thus, a chronically opacified sinus cavity can be falsely interpreted as "clear" on MRI (24,28,29). A significant sinus infection, such as a fungal rhinosinusitis, can also have this appearance. Because these uncommon but often important clinical scenarios may be occult by MRI, inflammatory sinus disease is best evaluated by CT and not MRI.
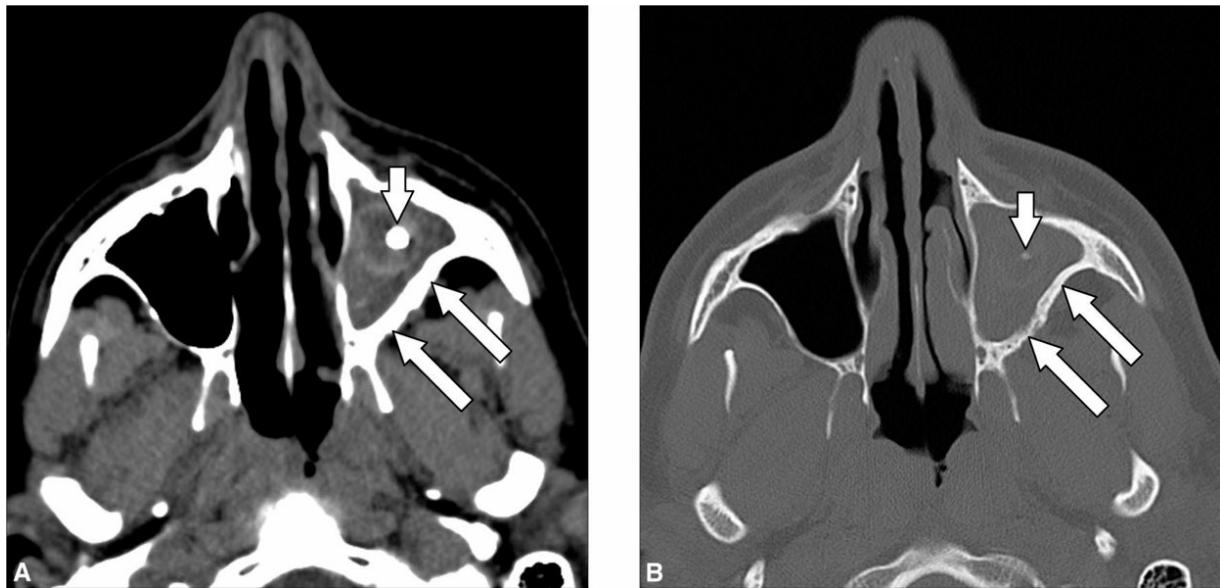
■ FIGURE 10.19 Mycetoma. An axial CT image viewed with soft tissue **(A)** and bone **(B)** windows demonstrates a completely opacified left maxillary sinus with a small focus of central mineralization (*small arrows*). Thickened and sclerotic left maxillary sinus walls (*medium arrows*) are consistent with chronic rhinosinusitis, in this case related to a mycetoma.

The modified Lund–Mackay classification for chronic rhinosinusitis can be used to stage the degree of sinus disease on CT (28–33). The classification system is based on sinus opacification (grades 0 to 2 for normal, partial or complete opacification, respectively), OMC obstruction (0 for no obstruction, 2 for obstruction), and the presence or absence of normal variants (0 or 1). Although most radiologists do not routinely use this classification system, a few studies have shown a positive correlation between the Lund–Mackay system and other markers of disease severity as well as helping determine the type of surgical management (33).

Abnormalities Associated with Rhinosinusitis

Retention Cysts and Sinonasal Polyps

A mucus retention cyst arises if there is obstruction of a solitary mucus gland duct (Fig. 10.21). A mucus retention cyst is a homogeneous, dome-shaped lesion, with a very thin wall that easily ruptures during surgery. It rarely fills the entire sinus cavity and does not cause sinus expansion. Serous retention cysts develop secondary to serous fluid accumulation beneath the submucosa (24,28). It is not possible to differentiate a serous retention cyst from a mucus retention cyst by imaging, although this has no clinical significance as both are benign and generally asymptomatic. On MRI, retention cysts are hyperintense in signal on

T2-weighted imaging (24,28). Unlike malignancies, retention cysts peripherally enhance but do not undergo central or homogeneous enhancement on MRI.

Sinonasal polyps are also associated with CRS. Polyps develop as a result of mucoperiosteal hyperplasia and abnormal accumulation of submucosal fluid. These lesions often appear as abnormal, rounded soft-tissue masses and therefore usually cannot be differentiated from retention cysts. However, if a pedunculated stalk is identified, then the diagnosis of a polyp can be made. Additionally, unlike retention cysts, polyps are most commonly located in the nasal cavity (Figs. 10.22 and 10.24). Small, isolated polyps are of little clinical concern, although if large or multiple, they may cause obstruction of a drainage pathway or nasal cavity. When a large solitary polyp arises in the maxillary antrum and extends through the ipsilateral infundibulum (or an accessory maxillary sinus ostium), it can terminate in the middle meatus or further extend into the choana. When it terminates in the middle meatus, it is termed an *antromeatal polyp*, and when it extends into or through the nasal choana, it is termed an *antrochoanal polyp* (Fig. 10.23). There is usually expansion of the infundibulum or accessory maxillary sinus ostium through which the polyp traverses. An antrochoanal polyp may protrude into the nasopharynx and mimic a mass originating in the nasopharynx. In order to prevent recurrence of an antromeatal or antrochoanal polyp, surgery requires resecting not only the protruding nasal cavity portion of the polyp but also its intrasinus component (34).
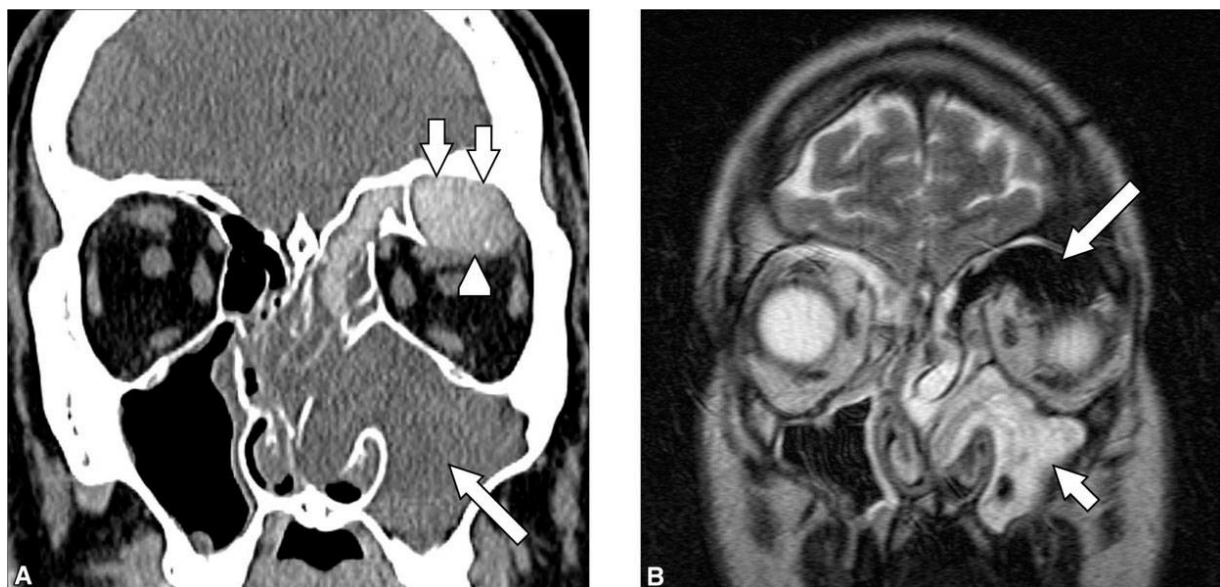
■ **FIGURE 10.20** Mucocele. A coronal CT image viewed with a soft tissue window through the frontal and maxillary sinuses **(A)** demonstrates a completely opacified left frontal sinus (*small arrows*) and left maxillary sinus (*medium arrow*) associated with sinus expansion, compatible with mucoceles. There is

dehiscence along the inferior wall of the left frontal sinus resulting in extension of the mucocele into the superior aspect of the left orbit (*arrowhead*). The increased attenuation in the left frontal sinus is related to inspissated secretions and/or fungal colonization. A coronal T2-weighted MR image of the same patient through the same level **(B)** demonstrates decreased signal in the left frontal sinus mucocele (*medium arrow*) because of sinus inspissation and/or fungal colonization. The increased signal in the left maxillary sinus mucocele (*small arrow,* **B**) reflects this mucocele's relatively higher water content.

Mucocele

A mucocele (Figs. 10.20 and 10.24) is an obstructed, expanded, and completely mucus-filled sinus that occurs with chronic sinus outlet obstruction (24,35). The accumulation of mucus under pressure results in sinus wall remodeling. A mucocele represents the most common expansile lesion of the paranasal sinuses. Mucoceles are typically solitary, although they may also be multiple. Mucoceles most commonly occur in the frontal sinuses (approximately 60%) where they can remodel the orbit and result in proptosis. The ethmoid air cells are the second most commonly involved site for mucocele formation (20% to 25%), followed by the maxillary and rarely the sphenoid sinuses (36). Initially, a mucocele may be indistinguishable from a completely opacified sinus related to rhinosinusitis. However, with time, there is expansion of the sinus cavity and osseous remodeling. Focal sinus wall lytic changes may also occur, resulting in wall dehiscence. Sinus contents may bulge through osseous defects into adjacent regions, and these osseous changes may mimic sinus malignancy on CT. Although a mucocele may resemble a neoplasm on CT, differentiating a simple mucocele from a malignancy is usually straightforward by MRI. The MRI appearance of a mucocele depends on the relative water and protein concentration of its contents. Generally, mucoceles are isointense on T1 and hyperintense on T2. The more the water content, the more T2 hyperintense a mucocele will be on MRI. Following intravenous administration of gadolinium, an MRI contrast agent, a mucocele may undergo mild peripheral but no central enhancement, whereas a sinus neoplasm more commonly solidly enhances or may heterogeneously enhance when necrosis is present (24,36). However, if a mucocele becomes superinfected (termed a *mucopyocele*), differentiation from a malignancy may be difficult.
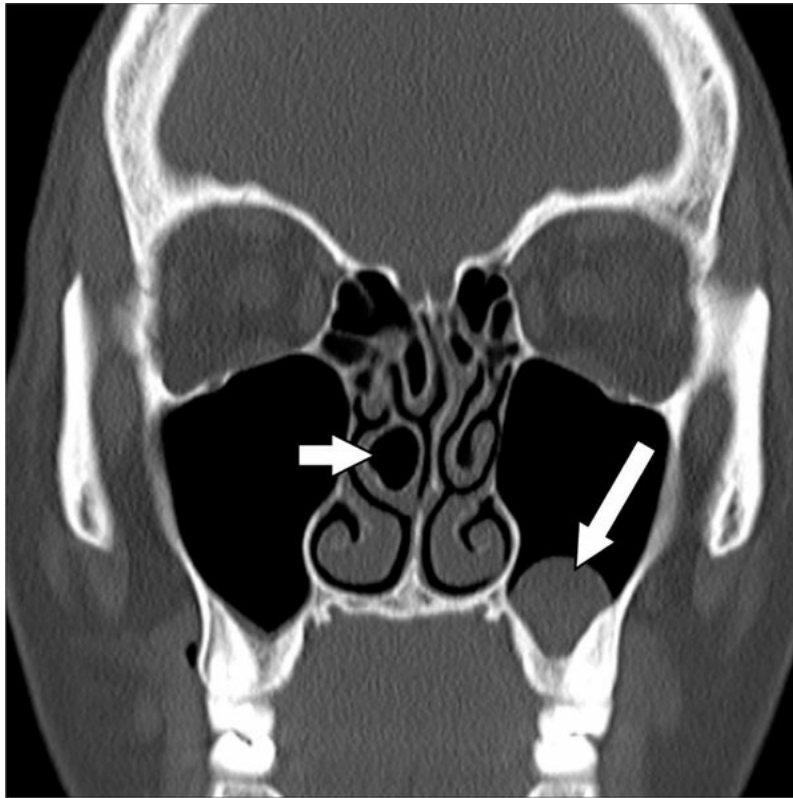
■ FIGURE 10.21 Retention cyst. A coronal CT image viewed with a bone window demonstrates a small dome-shaped structure along the floor of the left maxillary antrum, consistent with a small retention cyst (*medium arrow*). This could also represent a small sinus polyp, although there is no clinical relevance in distinguishing between these entities. A concha bullosa involving the right middle turbinate is also present (*small arrow*).
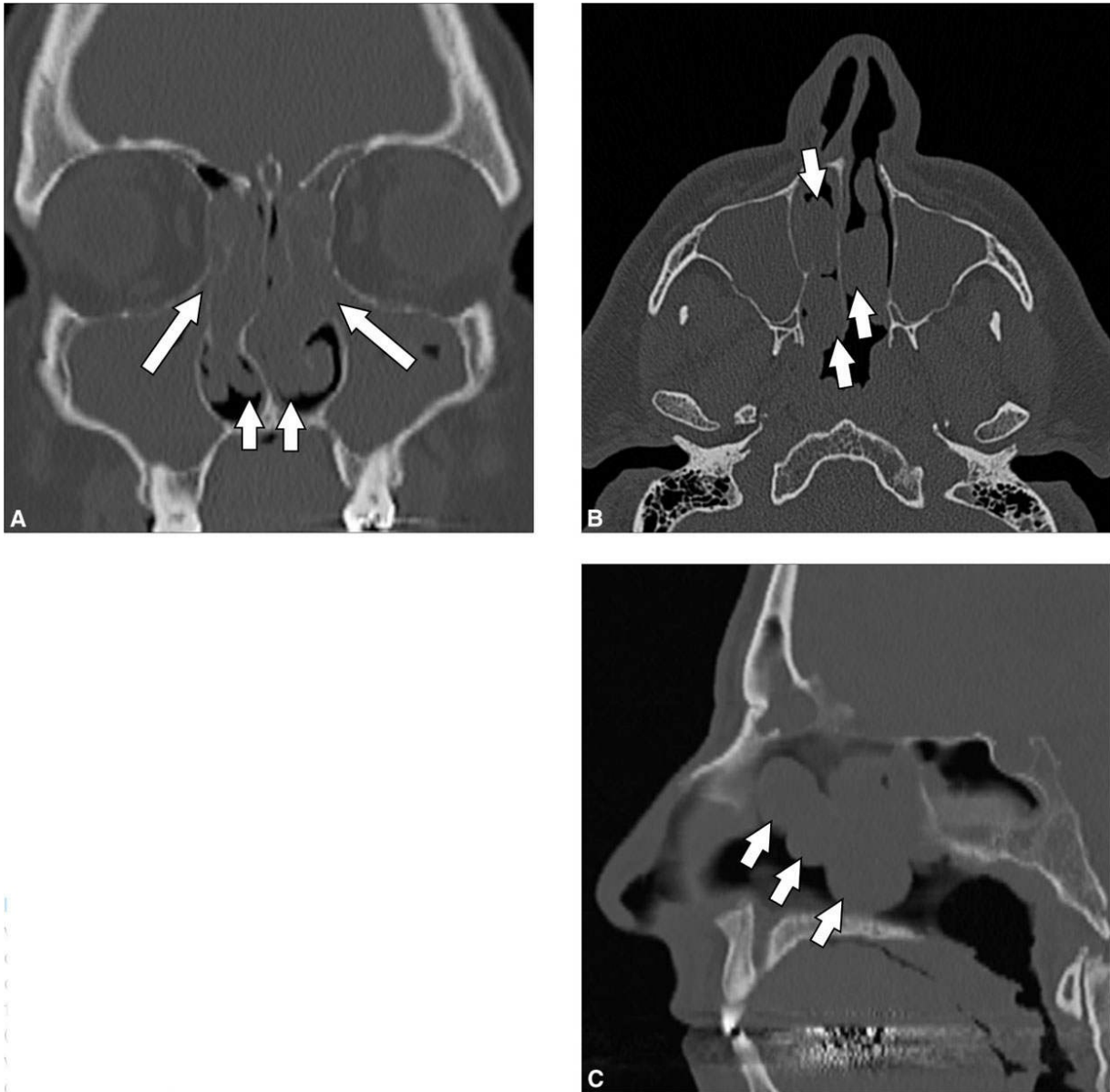
■ FIGURE 10.22 Sinonasal polyposis. A coronal CT image viewed with a bone window **(A)** demonstrates multiple polypoid opacities (*small arrows*) in the nasal cavity that are poorly delineated because they are closely apposed to the adjacent turbinates. The ostiomeatal complexes are opacified bilaterally (*medium arrows*). Axial **(B)** and sagittal **(C)** CT images viewed with a bone window also demonstrate the multiple polypoid opacities in the nasal cavity (*small arrows*).
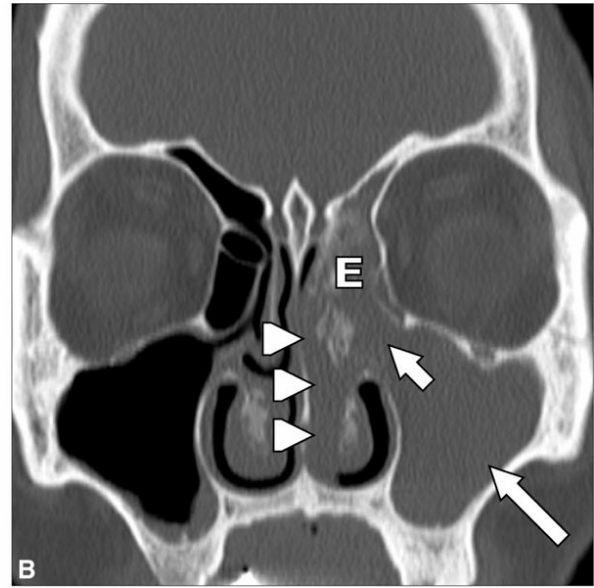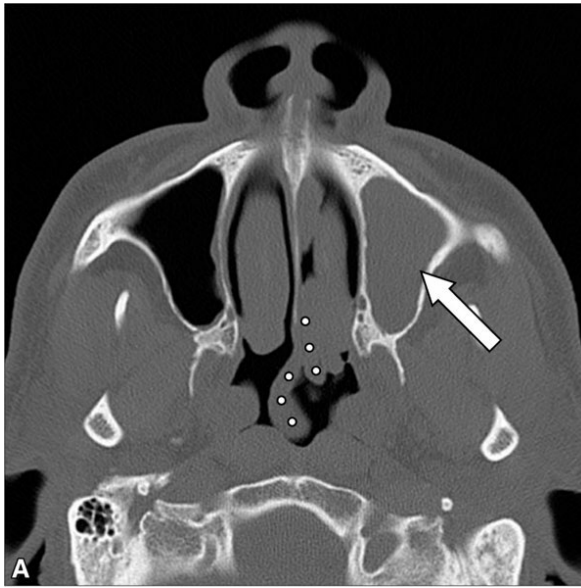
FIGURE 10.23 Antrochoanal polyp. Axial **(A)** and coronal **(B)** CT images viewed with a bone window demonstrate complete opacification of the left maxillary antrum (*medium arrows*). The left infundibulum is opacified and widened (*small arrow*) and the polypoid opacity extends medial to the left-middle and inferior turbinates (*arrowheads*). Contiguous polypoid opacity is present extending through the left nasal choana and into the nasopharynx (*dots*). The left ethmoids air cells (labeled *E* on image **B**) are opacified as well, because of fluid, mucosal thickening, or additional polyps.
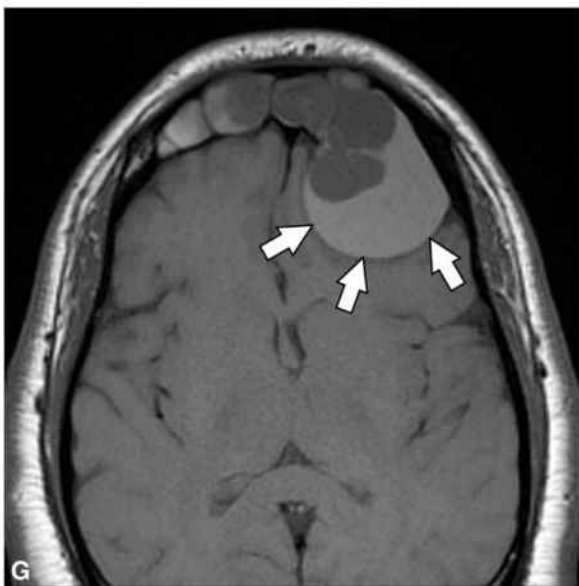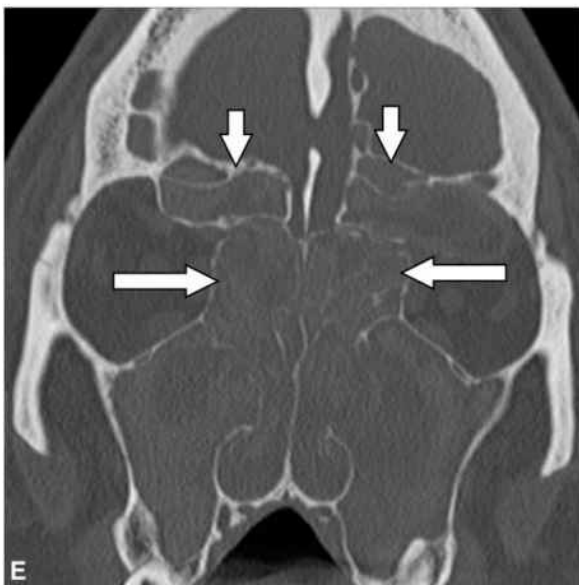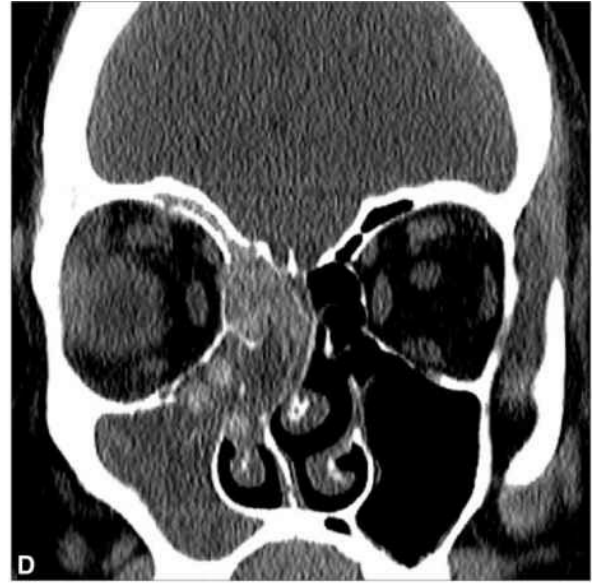
■ FIGURE 10.24 Allergic fungal sinusitis. Axial CT images viewed with a bone window through the level of the maxillary sinuses **(A)** and ethmoid air cells **(B)** demonstrate complete opacification of the right maxillary antrum (*medium arrow*) and ethmoid air cells (*dots*), with associated sinus expansion. Axial **(C)** and coronal **(D)** CT images viewed with a soft tissue window demonstrate increased attenuation of the involved sinuses, consistent with fungal colonization. Allergic fungal sinusitis in a different patient **(E to H)**. A coronal CT image viewed with a bone window **(E)** demonstrates marked expansion of the ethmoid air cells (*medium arrows*) and the visualized frontal sinuses (*small arrows*) with complete opacification of the paranasal sinuses and nasal cavity. The nasal cavity opacification is likely because of confluent polyposis. An axial CT image viewed with a soft tissue window **(F)** demonstrates marked expansion of the left frontal sinus, representing mucocele formation, with an imperceptible inner table of the left frontal sinus (*small arrows*). The increased attenuation in the right frontal sinus is consistent with fungal colonization (*medium arrows*, **F**). Noncontrast axial T1 **(G)** and coronal T2 **(H)** MR images demonstrate the markedly expanded left frontal sinus with imaging characteristics consistent with a mucocele (*small arrows*). The mucocele results in mass effect upon the superior aspect of the left orbit (*medium arrow*, **H**).
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Silent Sinus Syndrome

Silent sinus syndrome (Fig. 10.25) is a progressive and gradual disorder whereby a hypoventilated maxillary sinus becomes atelectatic resulting in ipsilateral enophthalmos (posterior positioning of the globe in the orbit) and hypoglobus (caudal positioning of the globe compared to the contralateral globe) (37). Silent sinus syndrome occurs in the setting of chronic OMC obstruction. Because the maxillary sinus walls are fairly malleable, when there is chronic OMC obstruction, negative pressure in the maxillary sinus can result in inward retraction of the maxillary sinus walls (37). This inward retraction of the maxillary sinus walls is termed an *atelectatic maxillary sinus*. Since the floor of the ipsilateral orbit shares a common wall with the roof of the maxillary sinus, the floor of the orbit becomes caudally depressed in the setting of an atelectatic maxillary sinus, thereby increasing the overall volume of the orbit (38). The orbital contents subsequently sag into the depressed orbital floor, resulting in enophthalmos and hypoglobus. When enophthalmos and/or hypoglobus are present, the constellation of findings is termed *silent sinus syndrome*, since the enophthalmos and hypoglobus are generally painless. Visual acuity is typically unaffected in silent sinus syndrome (38), although diplopia can occur.

Atelectasis of the infundibulum occurs when the uncinate process becomes laterally positioned and immediately apposed to the inferomedial orbital wall, effectively obstructing the ostiomeatal complex. This often results in concomitant enlargement of the ipsilateral middle meatus. An atelectic infundibulum likely precedes and almost always coexists with an atelectic maxillary sinus.
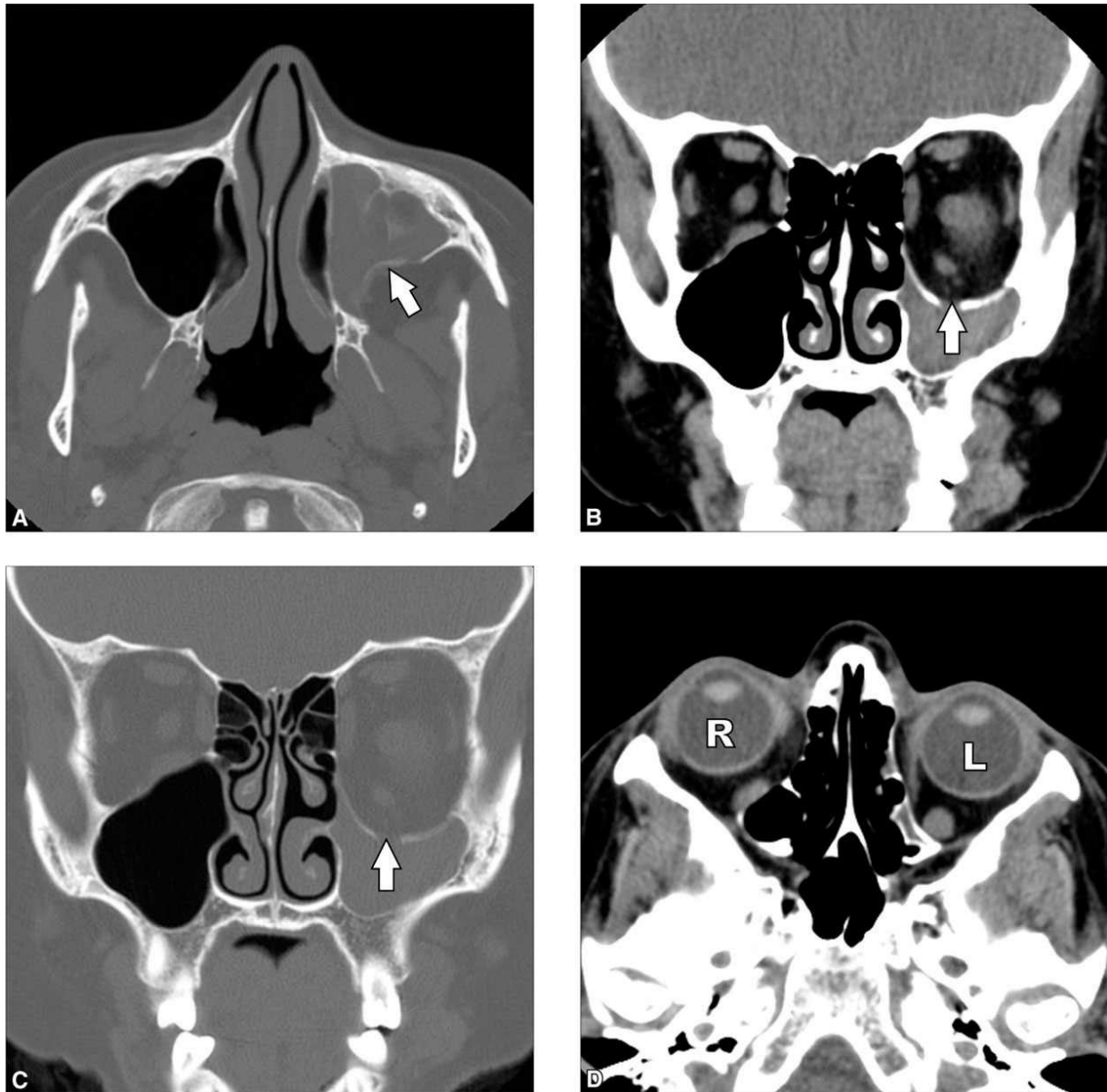
■ **FIGURE 10.25** Silent sinus syndrome. Axial CT image viewed with a bone window **(A)** demonstrates a completely opacified left maxillary antrum, with ventral bowing of the posterolateral maxillary sinus wall (*arrow*) and a smaller volume compared to the right maxillary antrum. Coronal CT images viewed with soft tissue **(B)** and bone **(C)** windows demonstrate caudal bowing of the left orbital floor (*arrows*) toward the completely opacified, small left maxillary antrum. An axial CT image through the orbits viewed with a soft tissue window

(D) demonstrates subtle enophthalmos of the left globe (*L*) relative to the right (*R*).

Odontogenic Rhinosinusitis

Odontogenic rhinosinusitis (Fig. 10.26) is thought to account for up to 10% to 12% of cases of maxillary rhinosinusitis (39). The most common causes of odontogenic rhinosinusitis include a dental abscess and periodontal disease that perforate the maxillary antral floor, intra-antral foreign bodies related to dental procedures, and maxillary antral perforation from a dental extraction (39). The patient may experience dental pain, headache, and anterior maxillary tenderness with odontogenic rhinosinusitis (39). The treatment requires management of the odontogenic abnormality as well as the rhinosinusitis, which generally includes both medical and dental surgical intervention (39).

Intracranial Complications of Rhinosinusitis

The incidence of intracranial complications from rhinosinusitis has markedly decreased in the past decades because of improved clinical management of these cases and imaging guidance for treatment planning. However, there are a range of complications that still occur including meningitis, epidural abscess, subdural empyema, brain abscess, cortical venous thrombosis, and dural venous sinus thrombosis (24,40,41).

Gallagher et al. (42) performed a chart review during a 5-year period of all patients admitted to their institution with one of the above diagnoses. They identified 176 cases of which 15 patients had 22 intracranial complications related to rhinosinusitis. The incidence of complications among this group was as follows: epidural abscess—23%, subdural empyema—18%, meningitis—18%, cerebral abscess—14%, superior sagittal sinus thrombosis—9%, cavernous sinus thrombosis—9%, and osteomyelitis—9%. Intracranial spread of rhinosinusitis can result from direct communication via congenital or traumatic dehiscences, bone erosion, or through normal foramina such as those seen in the cribriform plate. Additionally, the diploic space of paranasal sinus marrow contains veins that anastamose with the intracranial veins, also providing a route of spread to the intracranial compartment. These routes may permit the spread of infection without obvious bone destruction. Furthermore, orbital complications including preseptal cellulitis, postseptal cellulitis, and subperiosteal orbital abscess may occur via spread of infection through valveless ethmoidal veins (41).

■ **FIGURE 10.26** Odontogenic sinusitis. Axial **(A)** and coronal **(B)** CT images viewed with a bone window demonstrate significant periodontal disease surrounding a left maxillary molar tooth. Erosive changes (*small arrow*) and dehiscence of the floor of the left maxillary antrum (*arrowhead*) due to the periodontal disease and a periapical abscess are present. The dental disease must be addressed in order to effectively treat the patient's sinusitis.

Association of Allergy, Rhinosinusitis, and Polyposis

The exact relationship between allergy and rhinosinusitis has not been fully elucidated. It is believed that an IgE-mediated (type 1 hypersensitivity) response occurs within the nasal mucosa in response to an inhaled allergen. Nasal mucosal edema results in obstruction of the sinus ostia, decreased ciliary action, and increased mucus production with subsequent rhinosinusitis. One study demonstrated that those patients with CT findings of extensive sinus disease had more markers of allergy. Specifically, this group had a much higher prevalence of IgE antibodies to common inhalant allergens than a group of patients with limited sinus disease (43).

Sinonasal polyposis is the term used to describe extensive polyp disease (Fig. 10.22). As with rhinosinusitis, there is debate concerning the relationship of nasal polyps (NP) with allergy; while likely multifactorial, allergy is a suspected factor in the development of NP (44). The triad of aspirin intolerance, NP, and asthma is well documented and is now called aspirin exacerbated respiratory disease (AERD), which is discussed in Chapters 19 and 27 (45). Additionally, studies have shown that elevated mucosal IgE levels and eosinophilic inflammation are present in NP biopsy specimens from asthmatic patients

(46,47). It is reported that 3% to 70% of patients with NP develop asthma, whereas 4% to 32% of asthmatic patients have NP (44).

Regardless of the etiologic factor, the imaging appearance of polyposis can be quite dramatic. Rounded polypoid masses are often identified occupying the majority and sometimes all of the nasal cavity (unilateral or bilateral), occasionally extending into the adjacent paranasal sinuses. The involved ostia and outflow tracts are typically expanded by the polyps. The lateral walls of the ethmoid sinus (medial orbital walls) may bulge laterally. The osseous sinus walls may be thinned and at times appear dehiscent, raising the possibility of a malignant tumor. On CT, sinonasal polyposis is generally low in attenuation, although high attenuation can sometimes be seen surrounding the polyps. On MRI, the appearance of sinonasal polyposis will depend on the relative free water and protein concentration within the polyps. Following intravenous administration of gadolinium contrast, polyps enhance peripherally, similar to what is identified with retention cysts, but not diffusely, as would be seen with malignancies (48).

GRANULOMATOUS DISEASES

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA), formerly known as Wegener granulomatosis, is an idiopathic necrotizing granulomatous vasculitis that can involve virtually any organ system, including the paranasal sinuses and in particular the nasal cavity (26,49) (Fig. 10.27). Common, but nonspecific, imaging findings seen with GPA include nodular mucosal thickening, osseous destruction, osseous sclerosis, and nasal septal perforation. An orbital mass or extension of granulomatous disease from the paranasal sinuses into the orbit is the most common, extra-sinonasal head and neck lesion associated with GPA (48).

Sarcoidosis

Sarcoidosis is a systemic granulomatous disease that is characterized by noncaseating granulomas and multi-nucleated giant cells (26). Sarcoidosis is often indistinguishable from GPA by imaging and may result in osseous/cartilage destruction as well as nasal septal perforation (Fig. 10.28). Occasionally, nodules representing noncaseating granulomas can be identified along the nasal septum (26).

Advanced cases of granulomatosis with polyangiitis and sarcoidosis can

result in a so-called *saddle-nose* deformity, where the dominant abnormality is nasal bridge depression from cartilage and osseous destruction (Fig. 10.27).

FUNGAL RHINOSINUSITIS

Fungal rhinosinusitis can be divided into four categories: allergic fungal rhinosinusitis (AFRS), mycetoma (fungal ball), chronic invasive fungal rhinosinusitis (CIFR), and acute invasive fungal rhinosinusitis (AIFRS).
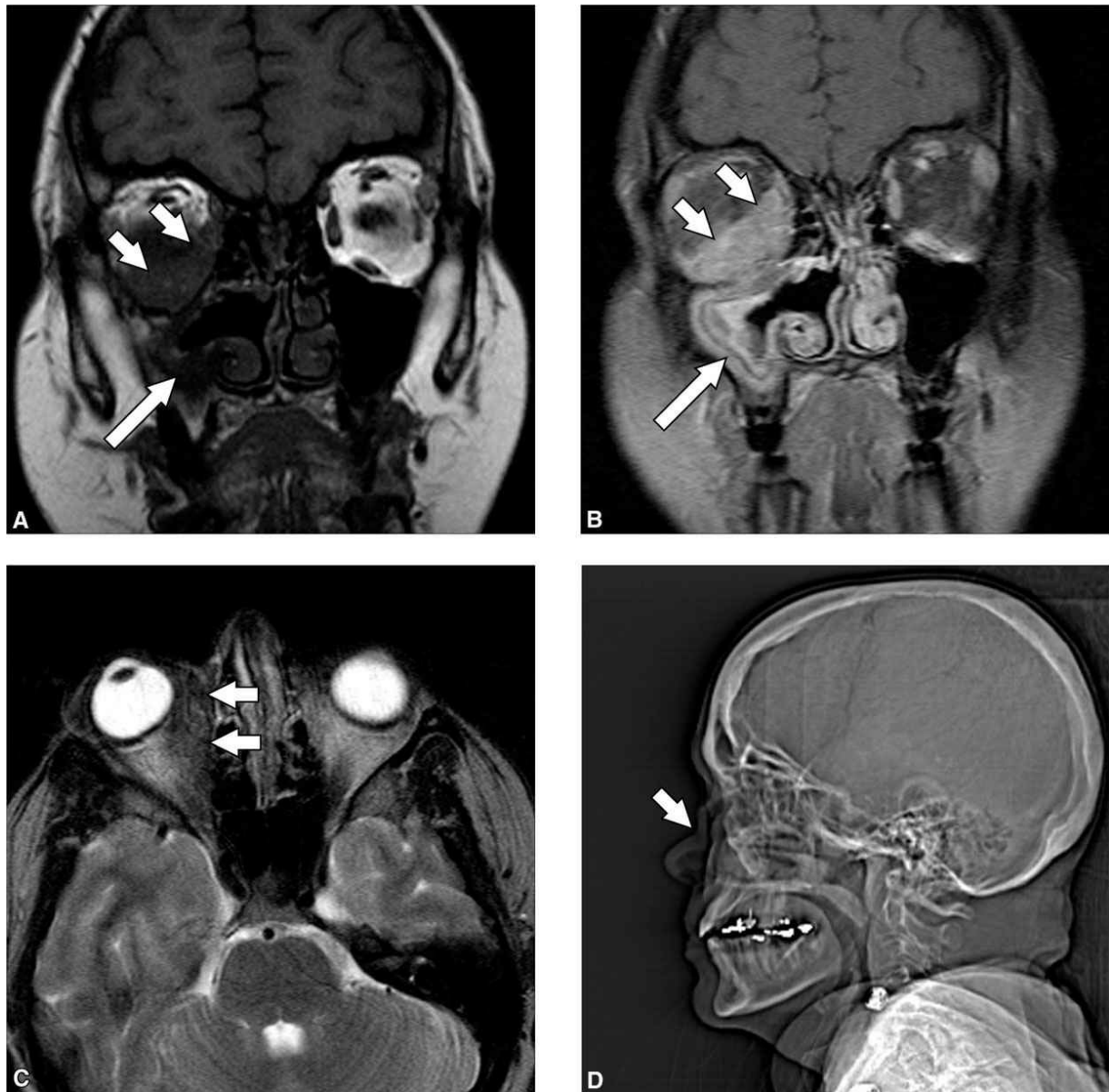
■ **FIGURE 10.27** Granulomatosis with polyangiitis. Coronal pre-contrast T1 **(A)** and post-contrast T1 fat suppressed **(B)** MR images demonstrate nonspecific enhancement of the right maxillary sinus (*medium arrows*) and the inferomedial right orbit (*small arrows*). An axial T2-weighted MR image **(C)** demonstrates the lesion in the orbit to be hypointense relative to fat (*small arrows*). There is associated lateral displacement of the right globe. Orbital involvement is often

the first extra-sinonasal manifestation of granulomatosis with polyangiitis. Lateral scout image **(D)** from a sinus CT of a different patient with the same diagnosis demonstrates a saddle nose deformity (*small arrow*).

Allergic Fungal Rhinosinusitis

AFRS occurs when fungi colonize the sinus of an atopic immunocompetent host and act as an allergen, eliciting both humoral and cellular immune responses. The inflammation results in obstruction of the sinus, stasis of secretions, and further fungal proliferation. The characteristic findings of AFRS include: fungal elements on pathology, characteristic CT findings, type I hypersensitivity, and eosinophilic mucin (50).

The characteristic imaging features of AFRS include completely opacified, multiple sinus involvement with associated sinus expansion, osseous remodeling and thinning, and sinus disease that contains high attenuation (Fig. 10.24) (36). The bone resorption and remodeling is because of pressure from the expanding allergic mucin mass rather than invasion of fungi into the sinus mucosa or bone (51). Most cases of AFRS are associated with nasal polyposis (51). The ill-defined high attenuation on CT is believed to be secondary to the presence of calcium, heavy metals (iron and manganese) and inspissated secretions. On MRI, the presence of calcification and/or paramagnetic ions within AFRS may result in decreased or completely absent T1 and T2 signal (35,52).
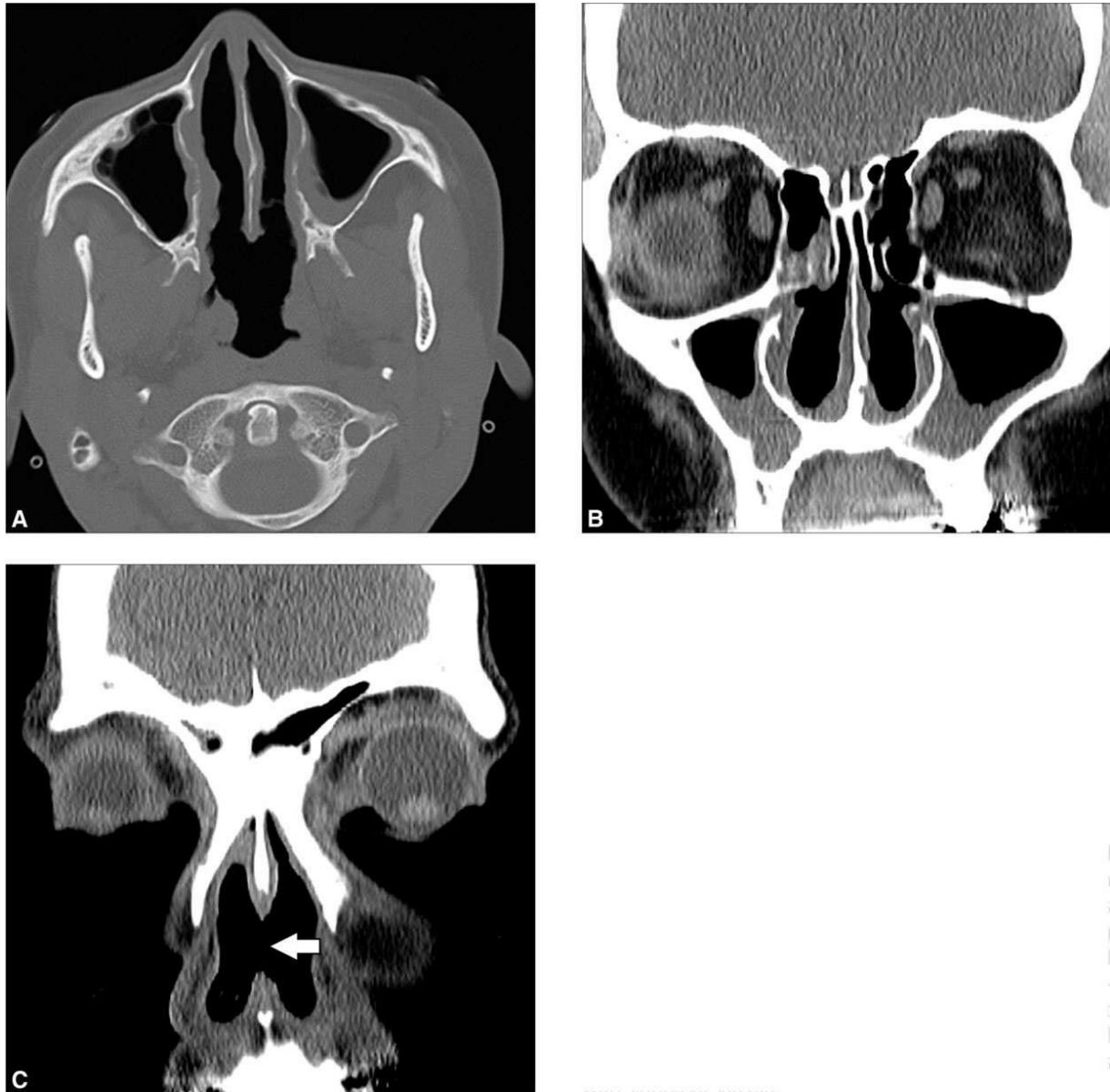
FIGURE 10.28 Sinonasal sarcoid. An axial CT image viewed with a bone window **(A)** and a coronal CT image viewed with a soft tissue window **(B)** demonstrate relatively featureless mucosa with scattered mucosal thickening as well as stranding in the nasal cavity and paranasal sinuses. The patient has had prior sinus surgery, including middle and inferior turbinectomies. Coronal CT image viewed with a soft tissue window at the level of the anterior nasal cavity **(C)** demonstrates a nasal septal perforation (*arrow*), which is often seen in patients with sinonasal sarcoid.

Mycetoma

A mycetoma (or fungal ball) is identified in nonatopic immunocompetent individuals. The fungus resides within the sinus secretions and does not penetrate the mucosa (51). A mycetoma is a tangled mat of hyphae that results in low-

grade, chronic, noninvasive fungal sinus disease. A mycetoma typically involves only one sinus, and the maxillary sinus is most commonly involved (53). Mycetomas generally result in sinus wall sclerosis (Fig. 10.19), do not result in osseous erosion, and are usually asymptomatic or only minimally symptomatic. A mycetoma often contains calcification or a concretion located within or near the center of the sinus opacification. MRI demonstrates intermediate T1-weighted signal and hypointense T2-weighted signal. However, as is seen with other fungal sinus disease processes, a mycetoma may be completely devoid of T1 or T2 signal.

Chronic Invasive Fungal Rhinosinusitis

CIFR is a rare entity, especially in the United States. It typically occurs in an immunocompetent individual, although immucompromised patients are susceptible. The fungus in this entity insidiously proliferates over a course of months to years and penetrates the sinus mucosa, osseous walls, and may invade the adjacent vasculature (54). Like AIFRS, CIFR may be fatal if left untreated. Indeed, many of the same complications, imaging findings, and offending organisms that occur with AIFRS may also be identified with CIFR. However, the presence of osseous wall sclerosis, which may occur with CIFR (54), is a finding not typically associated with AIRFS.

Acute Invasive Fungal Rhinosinusitis

AIFRS is a rapidly progressive disease that occurs in the immunocompromised host, with *Aspergillus, Rhizopus,* and *Mucor* being the most common offending organisms (51). It usually results in soft tissue and vascular invasion with necrosis. While AIFRS may erode and destroy bone, the bone may be intact on imaging (Fig. 10.29). Silverman et al. (55) described loss of the normal periantral fat planes (i.e., premaxillary and retromaxillary fat pads) in some cases of AIFRS. This is because AIFRS can spread from the sinus lumen into the adjacent soft tissues via perivascular channels located within the diploic space of the paranasal sinus walls. The periantral fat plane infiltration that may occur with AIFRS reflects one of its earlier imaging findings and is a critical imaging finding in order to initiate prompt treatment of this highly invasive process. Typically, AIFRS is characterized by a heterogeneously enhancing mass with or without bone erosion/destruction. In addition to periantral fat infiltration, the infection may extend into other facial soft tissues, including the orbit, as well as extend intracranially. Because of its highly aggressive nature, AIFRS can be lethal if left untreated.

SINONASAL TUMORS

A definitive radiologic diagnosis of sinonasal neoplasms can be difficult on CT, particularly if there are no aggressive features, such as bone destruction or soft tissue invasion. Furthermore, the presence of bone destruction or soft tissue invasion is not specific for tumors, as these findings may occur with aggressive infectious processes. Most often, CT and MRI are complementary imaging modalities when evaluating tumors. On MRI, tumors are most often intermediate to low in signal intensity on T2-weighted images. In contradistinction, non-inspissated secretions, polyps, and retention cysts are generally hyperintense on T2-weighted imaging. Neoplasms often enhance centrally, either in a homogeneous or heterogeneous pattern, whereas mucosal thickening related to rhinosinusitis, polyps, retention cysts, and mucoceles do not. The combination of these T2-weighted and post-contrast MR imaging characteristics are critical in differentiating tumors from these benign entities and provide a "map" for the surgeon of what represents tumor versus post-obstructive sinus disease.

The most common, benign sinonasal tumor is the osteoma (Fig. 10.30) (56). An osteoma is a well-defined, bone-forming tumor (48) covered by mucosa. It is most commonly located in the frontal sinus (56) but can be seen in any sinus. An osteoma is generally an incidental asymptomatic finding, unless an osteoma results in sinus obstruction, such as may occur when strategically located within the frontoethmoidal recess. Rarely, a sinus osteoma may also be associated with spontaneous pneumocephalus. If multiple osteomas are present, one should consider Gardener syndrome, which is an autosomal dominant condition of multiple osteomas, colorectal polyps, and soft tissue tumors (56).

An inverted papilloma is an epithelial tumor that typically occurs in 50- to 70-year-olds, with a male to female ratio of 3:1 (56). This tumor is unusual in that the epithelium grows (inverts) into the underlying stroma, rather than initially growing exophytically. It is usually a unilateral mass that arises from the lateral nasal wall adjacent to the middle turbinate and commonly extends into the maxillary sinus. An inverted papilloma is locally aggressive and often recurs following local resection. There is an association between an inverted papilloma and synchronous carcinomas; that is, carcinomas which arise from or in conjunction with an inverted papilloma. Squamous cell carcinoma is the most common carcinoma in this setting, with this malignancy found in a mean of 7% of cases of inverted papilloma (57). Squamous cell carcinoma may also arise following resection of an inverted papilloma, which is termed a metachronous tumor, although metachronous tumors are much less common that synchronous

tumors (56). On CT, an inverted papilloma is primarily a soft tissue density lesion that may have a lobulated surface and contain foci of calcification. On MRI, the classic appearance is that of a "cerebriform" pattern (i.e., curvilinear striations) on T2-weighted and contrast-enhanced imaging (Fig. 10.31) (48). At surgery, these lesions are often gritty in consistency, as opposed to polyps, which are soft. Given the proclivity of an inverted papilloma for local destruction, as well as its association with malignancy, surgery is part of the treatment paradigm (56), often with wide surgical margins.
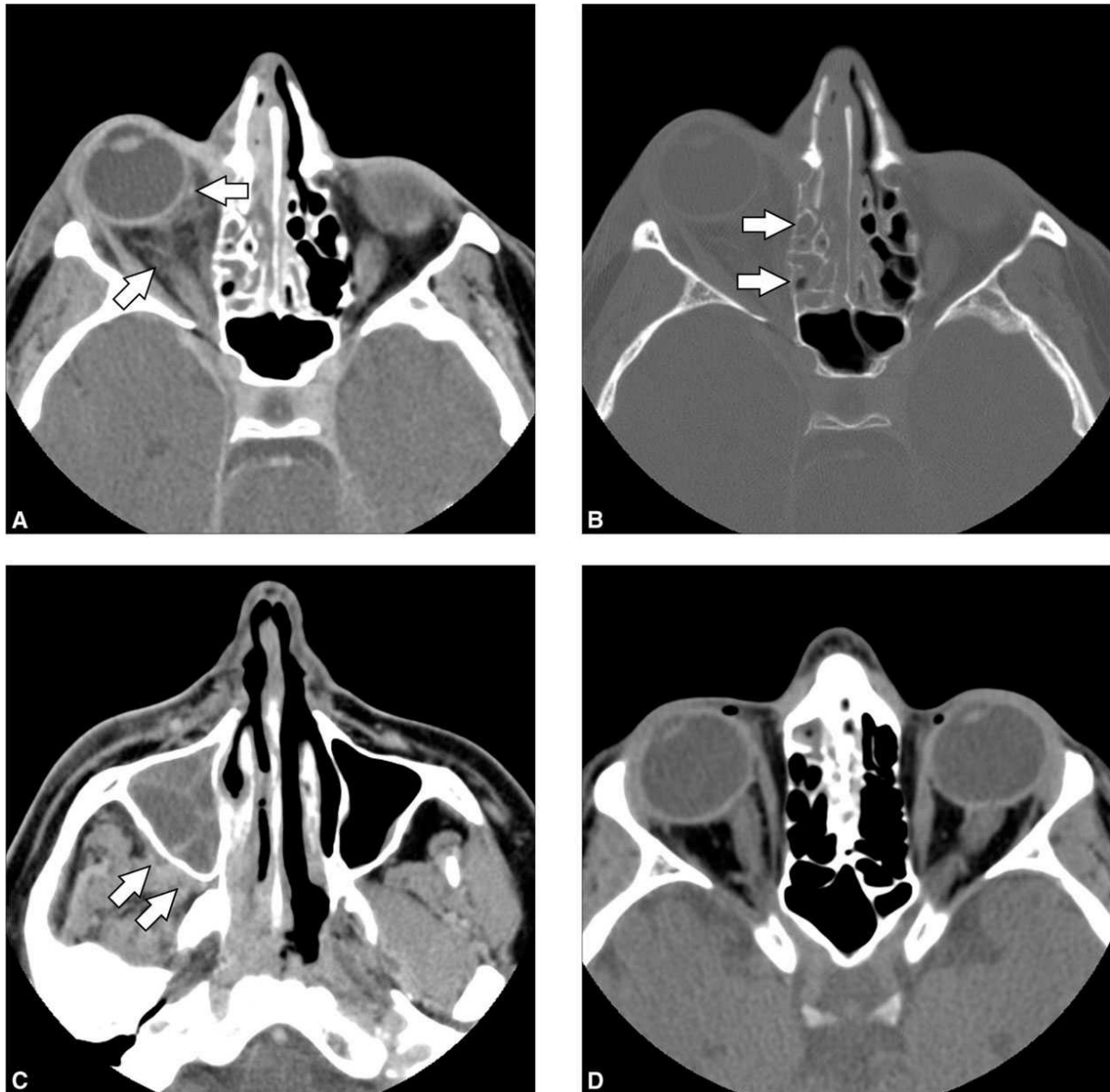
■ **FIGURE 10.29** Invasive fungal sinusitis (IFS). Axial CT image viewed with a soft tissue window through the orbit **(A)** demonstrates opacification of the right ethmoid air cells and right orbital cellulitis because of invasion of the fungal disease into the right orbit (*arrows*). Axial CT image viewed with a bone window through the orbit **(B)** demonstrates that the medial right orbital wall is

intact (*arrows*). IFS can spread via small osseous channels without resulting in osseous destruction. Axial CT image viewed with a soft tissue window through the maxillary sinus **(C)** of the same patient demonstrates IFS spreading into the right retromaxillary fat (*arrows*), again demonstrating the transosseous extension without bone destruction. An axial CT image viewed with a soft tissue window **(D)** through the orbit 2 days prior reveals a normal appearing orbit. This case demonstrates the aggressive nature of IFS and the high clinical suspicion that is needed to diagnose this entity.

A juvenile nasopharyngeal angiofibroma (JNA) is a benign vascular neoplasm that is unencapsulated (48). A JNA is generally thought to arise in the sphenopalatine foramen (56) and almost always involves the pterygopalatine fossa. This tumor usually presents in the second decade of life, often with epistaxis and/or nasal obstruction, and it occurs nearly exclusively in males. Although a JNA is histologically benign, it is locally aggressive. It commonly widens and destroys the pterygopalatine fossa and erodes the pterygoid plates as it extends into the nasopharynx. The characteristic location, often with destruction or ventral bowing of the posterolateral wall of the maxillary sinus, is one of the specific features that can be identified on CT (Fig. 10.32). In addition, the tumor is highly vascular and will contain extensive vascular flow voids on MRI and high flow architecture on magnetic resonance angiography, CT angiography, and conventional angiography (58). Tumor vascular supply often arises from the internal maxillary and ascending pharyngeal branches of the external carotid artery. When a JNA extends intracranially, small branches from the cavernous internal carotid artery may supply the tumor.

■ **FIGURE 10.30** Osteoma. Coronal **(A)** and axial **(B)** CT images viewed with a

bone window demonstrate a large osteoma (*arrows*) in the right frontal sinus. The osteoma has a pedunculated appearance on the axial image **(B)**. Osteomas are typically asymptomatic, although they can result in sinus obstruction.

Malignancies of the nasal cavity and paranasal sinuses are rare. When they do arise, they most often involve the maxillary sinus, followed by the ethmoid air cells, and lastly the nasal cavity. Eighty percent of all sinus malignancies represent squamous cell carcinoma (Fig. 10.33) (59). CT findings include bone erosion and destruction with extension of the tumor beyond the sinus lumen or nasal cavity. MRI has a clear advantage relative to CT in evaluating sinus malignancies, including aiding in differentiating tumor from post-obstructive sinus disease, as discussed previously. MRI can also help delineate the extent of the tumor and assess for invasion into adjacent structures. CT is complementary to MRI by providing improved osseous detail relative to MRI.

Other sinonasal malignancies that occur with variable frequency are esthesioneuroblastoma, sinonasal undifferentiated carcinoma (SNUC), osteosarcoma, non-Hodgkin lymphoma, minor salivary gland tumors, and melanoma, to name a few. Many of these tumors do not have specific imaging findings.

An esthesioneuroblastoma is a neural crest tumor that arises from the olfactory epithelium of the nasal cavity. There is a bimodal age distribution, affecting teenagers and individuals in their sixth decade. These tumors are typically located in the superior aspect of the nasal cavity near the cribriform plate. When these tumors extend intracranially, they may be associated apical cysts along their cephalad margin. Recurrence rates are relatively high, occurring in approximately 50% of cases, although the 10-year survival rate is estimated at 50% to 70% (60). Esthesioneuroblastomas are typically hypointense on T1-weighted imaging, isointense to hyperintense on T2-weighted imaging, and enhance on postcontrast T1-weighted imaging (60). These tumors metastasize to the neck in 20% to 25% of cases; therefore, a neck CT is often indicated to evaluate for regional metastatic disease (60).

A SNUC (Fig. 10.34) is believed to be part of a spectrum that includes esthesioneuroblastoma (least malignant), neuroendocrine carcinomas, and small-cell carcinoma (most malignant) (61), although a SNUC is roughly equivalent in prognosis with neuroendocrine carcinomas (61). SNUC tumors usually arise in the nasal cavity and ethmoid air cells, and they are locally advanced when diagnosed (62). These tumors also have a high nuclear to cytosplasmic ratio.
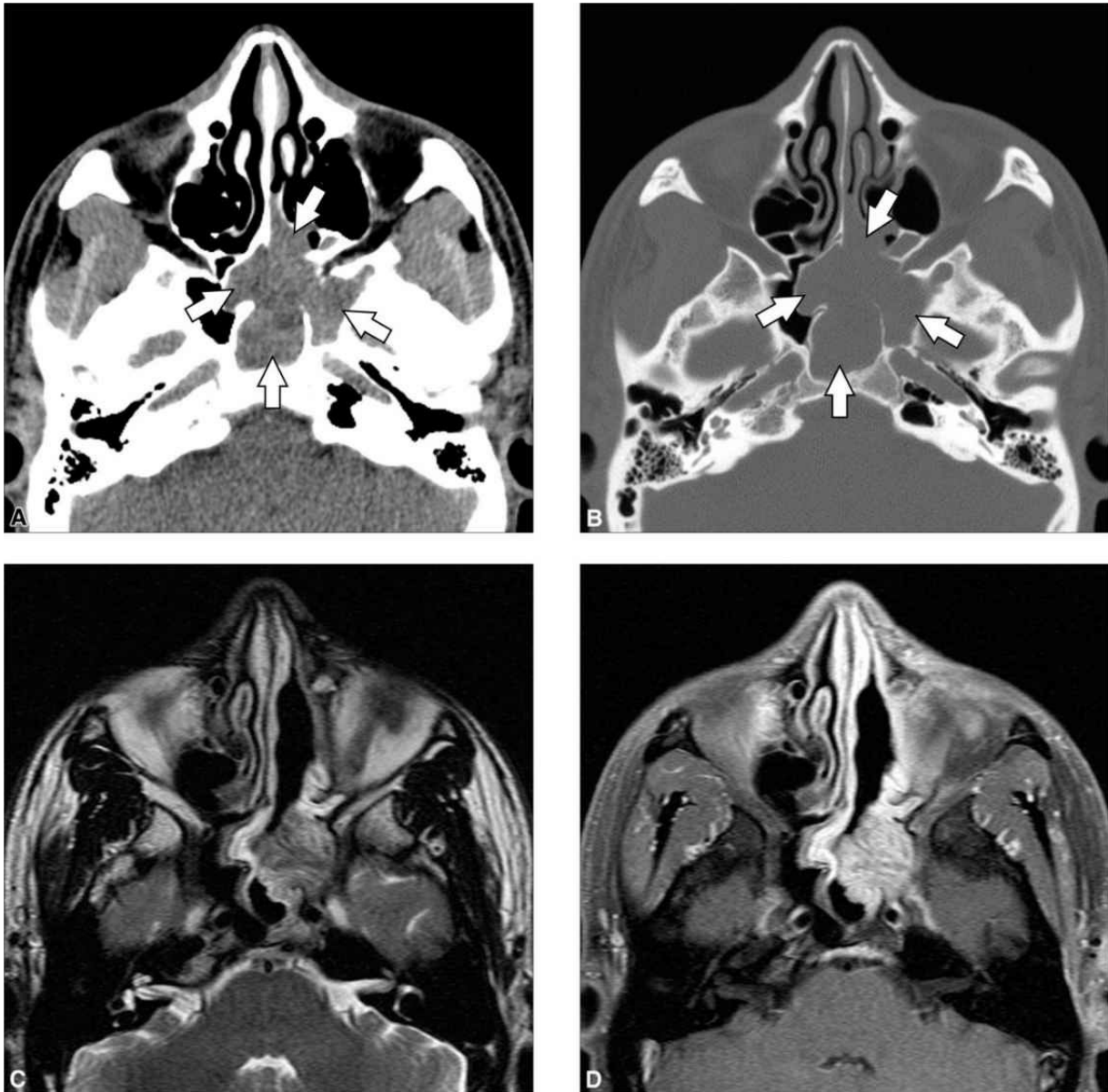
■ **FIGURE 10.31** Inverted papilloma. Axial CT images viewed with soft tissue **(A)** and bone **(B)** windows demonstrate nonspecific opacification of the sphenoid sinus and postero-superior left nasal cavity (*arrows*). Axial T2 **(C)** and axial post-contrast T1 fat suppressed **(D)** MR images following partial resection of the lesion demonstrate the "cerebriform" pattern that can be seen with inverted papillomas, characterized by the wavy, linear signal within the tumor.
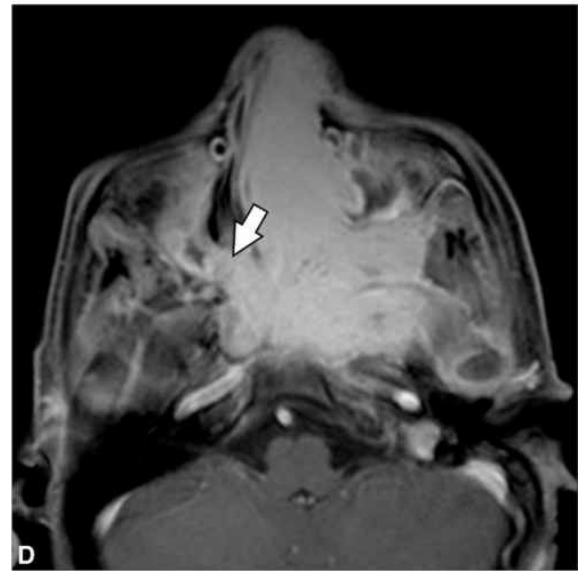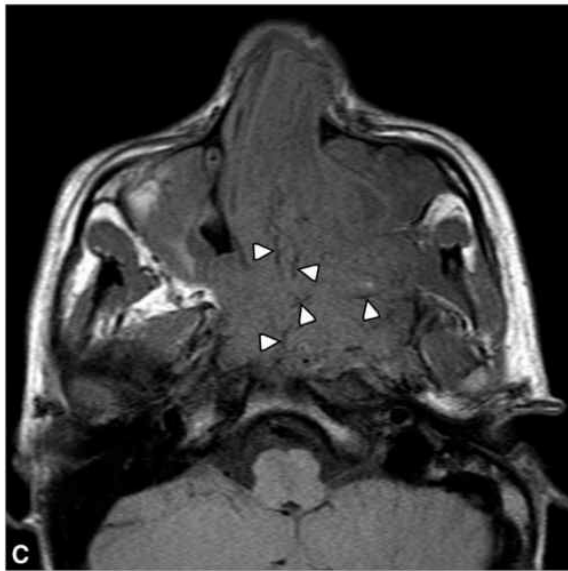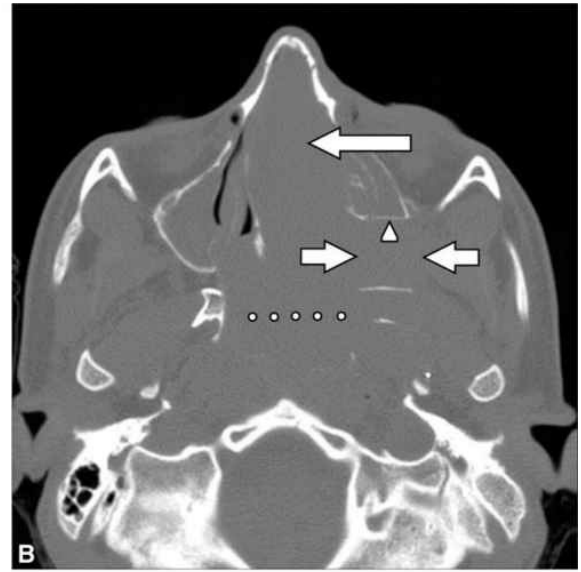
FIGURE 10.32 Juvenile nasopharyngeal angiofibroma. Axial CT images

viewed with soft tissue **(A)** and bone **(B)** windows demonstrate a large mass occupying and expanding the entire left pterygoplatine fossa (*small arrows*) and nasal cavity (*medium arrows*), with ventral displacement of the posterolateral left maxillary sinus wall (*arrowheads*). There is also complete opacification of the nasopharynx with suspected tumor (*dots*). Axial pre-contrast T1 **(C)** and axial post-contrast T1 fat suppressed **(D)** MR images demonstrate the mass to be markedly enhancing. There is also extension of the tumor into the right pterygopalatine fossa, best seen on the post-contrast image (*small arrow*, **D**). Notice the subtle flow voids seen on the pre-contrast T1-weighted image (*arrowheads*, **C**) indicating the hypervascular nature of these tumors. Axial T2-weighted MR image **(E)** of the same patient demonstrates diffuse, decreased T2 signal throughout the mass (*medium arrows*) consistent with high cellularity and decreased water content in the mass. High T2 signal in the bilateral maxillary antra (*arrowheads*, **E**) is consistent with sinus inflammatory disease, presumably post-obstructive owing to the mass.

■ **FIGURE 10.34** Sinonasal undifferentiated carcinoma (SNUC). Coronal pre-contrast T1 **(A)** and coronal post-contrast T1 fat suppressed **(B)** MR images through the frontal sinus and ethmoid air cells demonstrate a diffusely enhancing

mass that completely occupies the visualized left ethmoid air cells, left frontal sinus, left frontoethmoidal recess, and the right frontoethmoidal recess (*small arrows*). The right frontal sinus is hyperintense on pre-contrast T1-weighted MR imaging **(A)**, consistent with proteinaceous sinus inflammatory disease (*dots*). The lateral aspect of the left frontal sinus does not enhance on post-contrast T1-weighted MR imaging (*arrowhead*, **B**) and is hyperintense on coronal T2-weighted MR imaging (*arrowhead*, **C**), suggesting additional sinus inflammatory disease that is fluid consistency. Axial post-contrast T1-fat-suppressed MR image **(D)** demonstrates cortical destruction of the anterior (*small arrow*) and posterior (*medium arrows*) tables of the left frontal sinus, indicating this tumor's aggressive behavior.
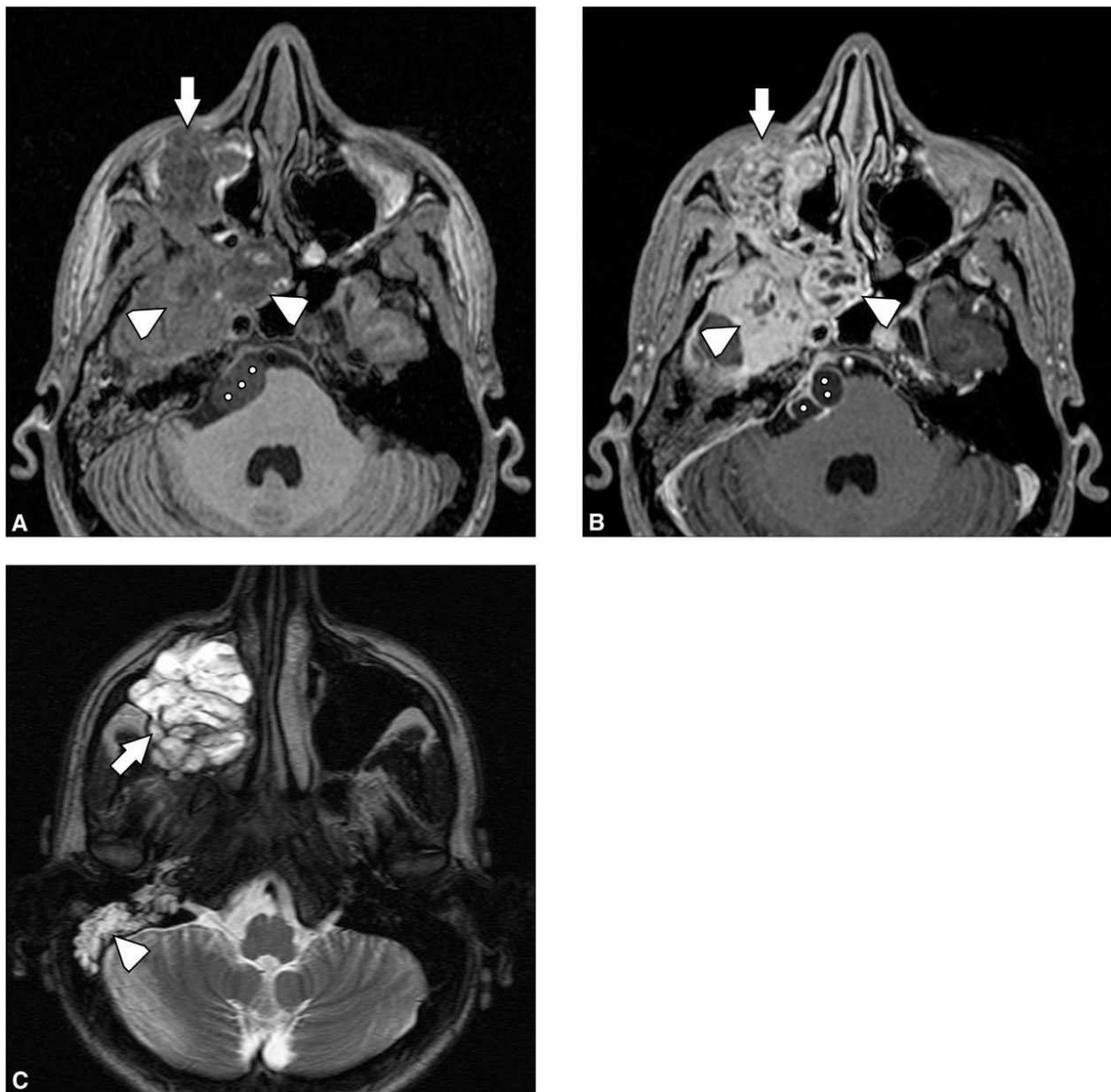
■ **FIGURE 10.35** Adenoid cystic carcinoma. Axial Magnetization Prepared Rapid Acquisition Gradient Echo (MP RAGE) pre-contrast T1 **(A)** and axial MP

RAGE post-contrast T1 **(B)** MR images demonstrate a markedly enlarged and heterogeneously enhancing mass involving the right maxillary antrum (*small arrows*), the right-middle cranial fossa and right Meckel cave (*arrowheads*), and the right prepontine cistern (*dots*). Axial T2-weighted MR image at the level of the right maxillary sinus **(C)** demonstrates heterogeneous, relatively hyperintense signal, which is often seen with adenoid cystic carcinoma (*small arrow*). The right mastoid air cells (*arrowhead*, **C**) are filled with fluid, either related to obstruction or dysfunction of the ipsilateral eustachian tube.

Adenoid cystic carcinoma (Fig. 10.35) accounts for 5% to 15% of sinonasal malignancies and arises from minor salivary glands located within the nasal cavity and paranasal sinuses (1,59,63). These tumors are locally aggressive neoplasms and are classically known for their propensity for perineural spread. Hematogenous spread to lungs and bones is relatively common, but metastatic disease to the lymph nodes is relatively uncommon (64).

Osteosarcoma (Fig. 10.36) is a malignant tumor that produces an osteoid matrix with many subtypes. This lesion may or may not be associated with a destructive pattern, and it generally produces dense sclerotic bone, particularly when it occurs in the maxillary sinus.

Melanoma of the nasal and sinus mucosa may have a unique MRI appearance that can suggest the diagnosis. Specifically, melanotic melanoma (as opposed to amelanotic melanoma) may be hyperintense on T1-weighted images and hypointense on T2-weighted images (59). Patients with sinonasal melanoma present with advanced disease and most succumb to the disease within 3 years of diagnosis (65).
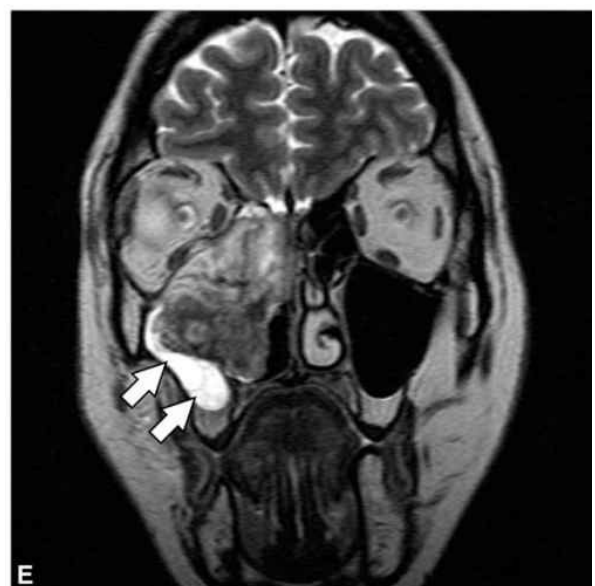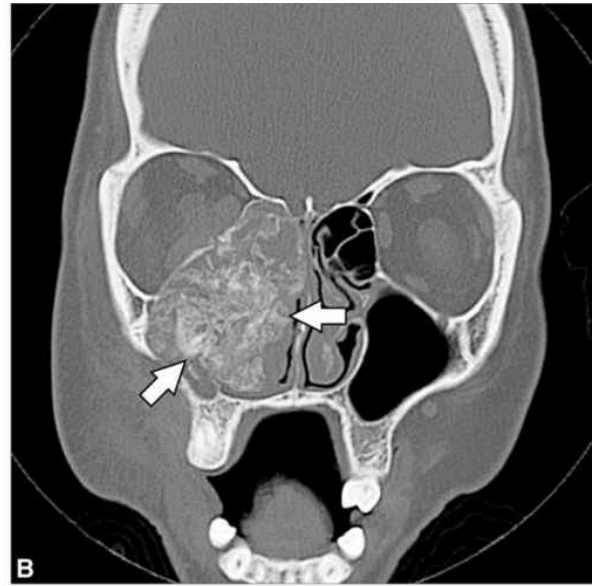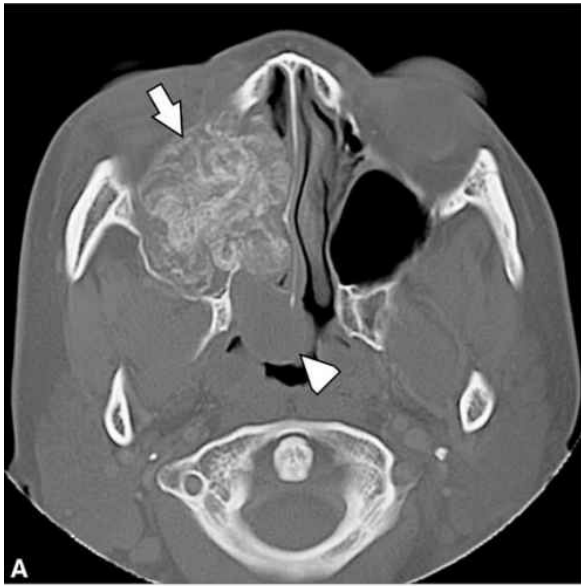
■ **FIGURE 10.36** Osteosarcoma. Axial **(A)** and coronal **(B)** CT images viewed with a bone window demonstrate a large osseous mass (*small arrows*) occupying the entire right maxillary antrum and extending into the right nasal cavity as well as the right ethmoid air cells. A soft-tissue component of the mass is seen extending into the nasopharynx (*arrowhead*). Coronal pre-contrast T1 **(C)** and coronal post-contrast T1 fat suppressed **(D)** MR images demonstrate the mass to be nearly completely enhancing. Coronal T2-weighted MR image **(E)** demonstrates the mass to be primarily hypointense, indicative of the tumor's high nuclear to cytoplasmic ratio and relatively low water content. Notice the obstructive sinus disease (*small arrows*, **E**) located in the inferolateral aspect of the right maxillary antrum, which is hyperintense on the T2-weighted image and is clearly delineated from the tumor. This demonstrates the superior ability of MR imaging over CT imaging to determine the true extent of the tumor.

■ CONCLUSION

Imaging examinations are designed to not only recognize acute disease processes but also identify anatomic variations that may predispose to infection, which is best evaluated with CT. The anatomical guidance provided by cross-sectional imaging helps map out a course of action for the surgeon and aids in identifying potential areas at risk for complications. Although rhinosinusitis is a clinical diagnosis, there are imaging correlates. In addition, the complications related to a disease process or from surgery are best assessed by imaging studies. The exact relationship of allergy to the various inflammatory disease processes affecting the sinus remains unclear. Inflammatory disease processes can have a similar appearance to the more aggressive fungal and malignant entities; therefore, careful attention to the imaging findings, and clinical correlation, are required in order to differentiate these processes.

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Radiologic Evaluation of Allergic and Related Diseases of the Lower Airway

HATICE SAVAS AND THOMAS GRANT

The radiographic appearance of thoracic manifestations of allergic and systemic immunologic disorders comprises a variety of abnormalities that are influenced by the pathophysiologic characteristics of the underlying disease. These disorders include allergic small airways diseases, collagen vascular diseases, and the systemic vasculitides. The clinician must also be familiar with the diseases in this category, a diverse group, including granulomatosis with polyangiitis (GPA), previously known as Wegener granulomatosis, asthma, allergic bronchopulmonary aspergillosis (ABPA) and bronchocentric granulomatosis, hypersensitivity pneumonitis (HP), eosinophilic lung diseases, drug-induced lung injury, and immunoglobulin G4-related disease (IgG4-RD).

Immunologic and allergic diseases of the lungs can manifest radiographically as diffuse or focal pulmonary parenchymal and airway abnormalities (1,2). In earlier stages of the disease, radiographs may be normal. Although chest radiographs are usually abnormal in advanced disease, characterization is frequently impossible. Thin-section computed tomography (CT) of the chest, preferably high-resolution computed tomography (HRCT), has become the most important imaging technique to confirm the diagnosis.

COMPUTED TOMOGRAPHY

Using multidetector CT (MDCT) changes the way in which radiologists perform and interpret studies of the thorax (3,4). Current-generation CT scanners with 16 or more detector rows can acquire isotropic volumetric data in a single breath-hold. For example, MDCT scanners can cover the entire chest with a <1 mm collimation (section of thickness) in less than 20 seconds. MDCT not only generates traditional axial images but can acquire volumetric data sets to view the computer-generated information in multiple nonaxial planes if desired (4). The volumetric acquired data makes CT ideal for detecting, characterizing, and

distinguishing among diseases of the lungs, mediastinum, and pleura.

HRCT involves obtaining narrow (<2 mm) collimation, a small field of view, and a high-spatial frequency reconstruction algorithm to obtain detailed images of the lungs. By using a very thin section, structural superimposition within the section of thickness is reduced, permitting optimal evaluation of lung detail. At our institution, the HRCT is typically performed with the patient in the supine position. Images are obtained in full inspiration from the apex to the diaphragm using 1.0 mm collimation. This is followed by a fewer number of inspiratory images obtained in a prone position. Expiratory images obtained at the end of exhalation are essential to look for air trapping which is very important for diagnosis of certain conditions, such as HP. HRCT can detect lung disease at an early and potentially treatable stage. Specific findings in HRCT may also be helpful in differentiating acute from chronic disease and optimizing the site for bronchoscopic or open lung biopsy (3–5). The HRCT findings of certain immunologic lung diseases are often so characteristic that a lung biopsy is not required (6,7).

The use of intravenous (IV) contrast is variable for chest CT examinations, based on the indication. The IV iodinated contrast should not be used when performing an HRCT to evaluate the lung parenchyma and small airways primarily, because subtle pulmonary findings may be obscured by intrapulmonary contrast. In addition, IV contrast adds little value to the interpretation of diffuse lung disease while exposing patients to the risks associated with the administration of iodinated contrast (8). IV contrast in chest CT is helpful to distinguish lymph nodes from pulmonary vessels, characterize pleural disease, demonstrate vascular components of an arterial venous malformation, and detect pulmonary emboli.

IV contrast should be avoided in patients with a creatinine level above 1.5 mg/dL. Some practices have advocated stratification of potential risk by estimated glomerular filtration rate instead of serum creatinine, because it is a better indicator of baseline renal function (9). Low osmotic contrast is now preferred because it has fewer side effects. Corticosteroid pretreatment supplemented with antihistamine, diminishes the risk of adverse reactions in patients with a previous anaphylactic reactions to contrast material.

COMPUTED TOMOGRAPHY ANATOMY

The lung is composed of lobes, segments, subsegments, secondary lobules, and acini (10,11). Each level contains an airway, a pulmonary artery, and a

supporting structure, the peribronchovascular interstitium. The airway is a branching series of 20 generations that leads to the alveoli.

The secondary pulmonary lobule is the smallest unit of lung structure marginated by connective tissue septa (12). These lobules measure 1 to 2.5 cm in size and are supplied by a small bronchial and pulmonary arteries. The secondary lobule can be identified in both normal and abnormal lungs and is one of the target structure in chest CT or HRCT interpretation, particularly for interstitial lung disease. There are distinct patterns of abnormality on HRCT that help to define acute and chronic infiltrative lung diseases (Tables 11.1 and 11.2).

Reticular opacities, as a reflection of intra- or interlobular septal thickening, result from thickening of the pulmonary interstitium by fluid, fibrosis, or other materials. Pulmonary fibrosis on HRCT is characterized by traction bronchiectasis and honeycombing. In usual interstitial pneumonia type lung fibrosis, detecting the honeycombing is very important for definite radiologic diagnosis, and it is most often observed peripherally at the lung bases (5,7). In chronic HP, the fibrosis is usually most severe in the mid or upper lung zones because it is mostly related to the inhalational damage (13,14). Cysts or rounded air-containing nodules are present in a number of acute and chronic lung diseases. Nodules in a centrilobular distribution, which is in the center of the secondary pulmonary lobule, can be seen in acute and subacute HP, pulmonary hemorrhage, cryptogenic organizing pneumonia (COP), infection, and respiratory bronchiolitis-associated interstitial lung disease (15).

Ground-glass attenuation is characterized by the presence of hazy increased attenuation of lung without obscuration of the underlying bronchial or vascular anatomy. If the vessels are obscured, the term consolidation is used. Ground-glass attenuation can result from interstitial thickening, airspace filling, or both. Although ground-glass attenuation is nonspecific, it usually indicates the presence of an active, potentially treatable disease.

RADIOLOGIC FINDINGS IN IMMUNOLOGIC LUNG DISEASE

Granulomatosis with Polyangiitis

GPA, previously known as Wegener granulomatosis, is a systemic autoimmune disease characterized by a necrotizing granulomatous vasculitis of the upper and lower respiratory tracts and kidneys. The histologic features are a necrotizing vasculitis of small arteries and veins and granuloma formation. The clinical triad

of classic GPA is pulmonary disease, febrile sinusitis, and glomerulonephritis (2,16,17). A limited form of GPA can be confined to the lungs. It is a disease that predominantly affects male patients. The imaging findings in most patients are multiple nodules or irregularly marginated masses with no zonal predominance that are seen in the majority of the patients either at presentation or during the course of the disease. Waxing and waning of the pulmonary nodules and masses are features of the disease. The nodules or masses are usually multiple but can be solitary in approximately 25% of cases. Cavitation of the nodules occurs in approximately 50% of cases. The cavities usually have irregular, thick walls (2). After treatment, the nodules or cavities may resolve completely or result in a scar. On CT examination, the nodules typically have irregular margins and often have a peribronchovascular distribution (Fig. 11.1). Peripheral, wedge-shaped areas of consolidation representing an infarct may be present.

A localized or diffuse area of airspace consolidation may be present; these areas usually represent pulmonary hemorrhage. Involvement of the trachea or bronchial walls usually consists of mucosal or submucosal granulomatosis thickening. Wall thickening is usually circumferential and can be smooth or nodular. Involvement of the posterior membrane of the trachea is important to distinguish GPA from other entities affecting the trachea, such as relapsing polychondritis and tracheobronchopathia osteochondroplastica (18). If the thickening becomes severe, narrowing of the lumen and eventually calcification also may occur (1,2).

TABLE 11.1 COMMON COMPUTED TOMOGRAPHIC (CT) FEATURES OF IMMUNOLOGIC LUNG DISEASES

CT FINDING	ABPA	HYPERSENSITIVITY PNEUMONITIS (HP)	EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)	GRANULOMATOSIS WITH POLYANGIITIS (GPA)
Ground-glass opacities		Acute		Present with cytotoxic drug treatment
Consolidating/air trappings			Consolidation	

Irregular linear opacities	Chronic			Common
Nodules	Centrilobular		0.5–3.0 cm in diameter	Common/cav...
Distribution	Central	Mid and lower lung	Peripheral	
Honeycombing fibrosis	Late stage (for ABPA)	Late stages chronic HP		Late
Bronchial abnormality	Bronchiectasis, mucoid impaction	Bronchiectasis in chronic HP	Wall thickening	Focal and diff... narrowing

ABPA, allergic bronchopulmonary aspergillosis.

TABLE 11.2 COMPUTED TOMOGRAPHIC (CT) APPEARANCE OF IMMUNOLOGIC/EOSINOPHILIC LUNG DISEASE

DISEASE	CT APPEARANCE
Granulomatosis with polyangiitis (GPA)	Multiple nodules or masses with or without cavitation, peripheral wedge-shaped areas of consolidation
Asthma	Air trapping on expiratory HRCT, bronchial wall thickening
Bronchocentric granulomatosis	Bronchiectasis, atelectasis, peripheral consolidation, ground-glass attenuation
Chronic eosinophilic pneumonia	Patchy unilateral or bilateral airspace consolidation, predominantly peripheral distribution, areas of ground-glass attenuation predominantly in the middle and upper lung zones

Acute eosinophilic pneumonia	Ground-glass attenuation, diffuse areas of ground-glass attenuation, defined nodules, smooth interlobular septal thickening
Eosinophilic granulomatosis with polyangiitis (EGPA)	Airspace consolidation, areas of ground-glass attenuation, peripheral predominance or random distribution, nodules, bronchial wall thickening or dilatation, interlobular septal thickening
ABPA	Bronchiectasis, mucous plugging, atelectasis, peripheral airspace consolidation or ground-glass attenuation
Simple pulmonary eosinophilia	Patchy unilateral or bilateral airspace consolidation, predominantly peripheral distribution, areas of ground-glass attenuation predominantly in the middle and upper lung zones, usually transient and migratory
Drug-induced eosinophilic pneumonia	Areas of ground-glass attenuation, airspace consolidation, nodules, irregular lines
Hypereosinophilic syndrome	Patchy areas of consolidation of nodules with or without pleural effusion
IgG4-related disease	Pseudotumor, large mass-like densities, organizing pneumonia, honeycombing fibrosis; hilar and mediastinal adenopathy

ABPA, allergic bronchopulmonary aspergillosis; HRCT, high-resolution computed tomography; IgG4, immunoglobulin G4.

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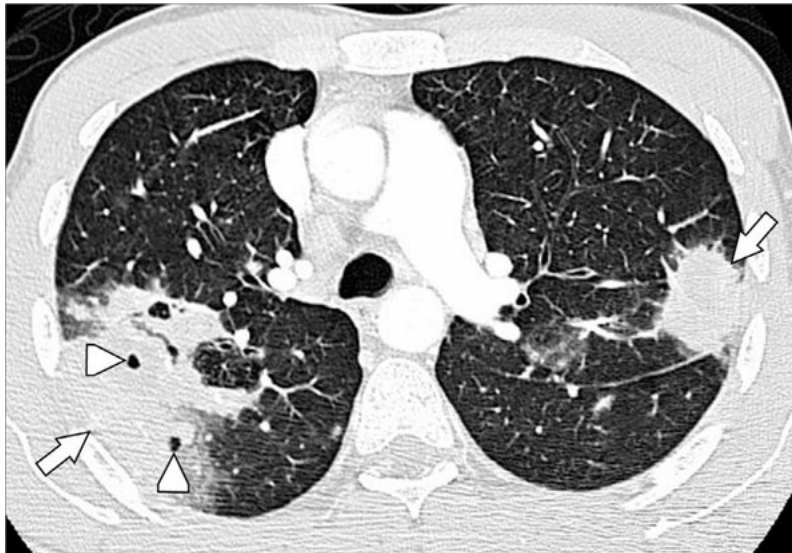
FIGURE 11.1 Granulomatosis with polyangiitis in a 26-year-old man who presented with chronic cough, hemoptysis, and weight loss. Computed tomography demonstrating bilateral irregularly marginated masses (*arrows*) and small areas of cavitation (*arrowheads*).

Asthma

HRCT findings of asthma have been assessed in several studies and include bronchial wall thickening, bronchial wall narrowing, and, to a lesser extent, bronchial wall dilatation (16). Mosaic attenuation, air trapping, and hyperinflation are common findings on HRCT. Emphysema is uncommon in the asthmatic nonsmoker. CT performed on expiration is helpful to determine the amount of air trapping (Fig. 11.2). Asthmatic patients with an forced expiratory volume in the first 1 second of less than 60% of the predicted value had more bronchial wall thickening and a lower bronchial arterial diameter ratio than did patients with normal airflow or only mild airflow obstruction. The use of HRCT with inspiratory and expiratory thin-section CT is of value in distinguishing asthmatic patients with normal-to-mild airflow obstruction from healthy subjects (19).
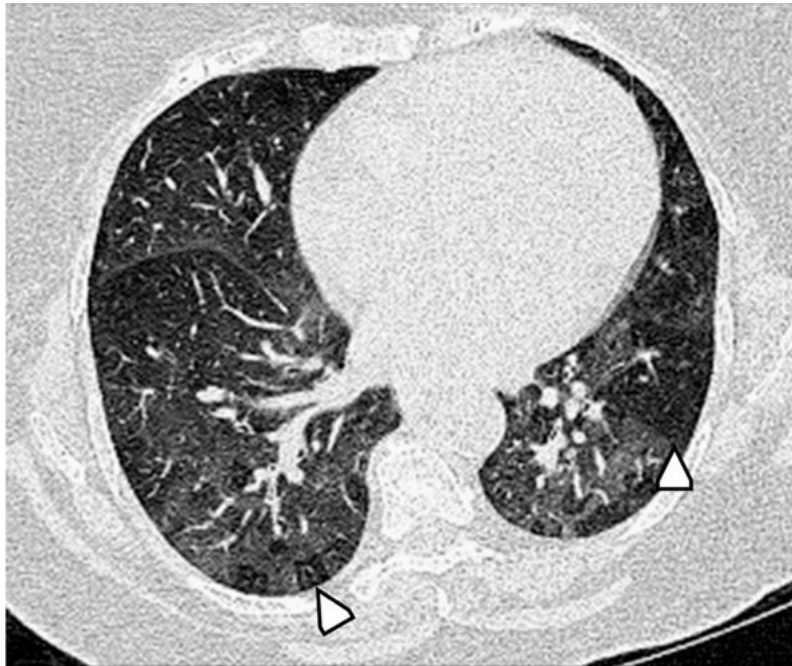
■ **FIGURE 11.2** Asthma in a 45-year-old man. Expiratory high-resolution computed tomography demonstrating bilateral focal air trapping (*arrowheads*).

Allergic Bronchopulmonary Aspergillosis and Bronchocentric Granulomatosis

ABPA is colonization of *Aspergillus fumigatus* in the chronic airway injury and almost exclusively seen in patients with asthma or cystic fibrosis. The primary radiographic presentation of ABPA on HRCT is severe bronchiectasis. The presence of bronchial dilatation, bronchial wall thickening, mucoid impaction, and centrilobular nodules in an asthmatic patient should strongly suggest the diagnosis of an ABPA (20,21). The diagnosis is even more likely if the bronchial dilatation is moderate to severe, affects three or more lobes, and involves the central bronchi (Fig. 11.3). If bronchial dilatation is present in asthmatic patients without ABPA, it is most often mild and has an upper lobe distribution. Several studies have concluded that HRCT is highly specific of ABPA when the classic findings are present in an asthmatic patient (16,21).

Bronchocentric granulomatosis often occurs in patients with ABPA and may be caused by *Aspergillus* species. It is characterized by a pattern of necrotizing granulomatous inflammation that destroys the walls of small bronchi and bronchioles (22). Imaging findings are similar to ABPA.

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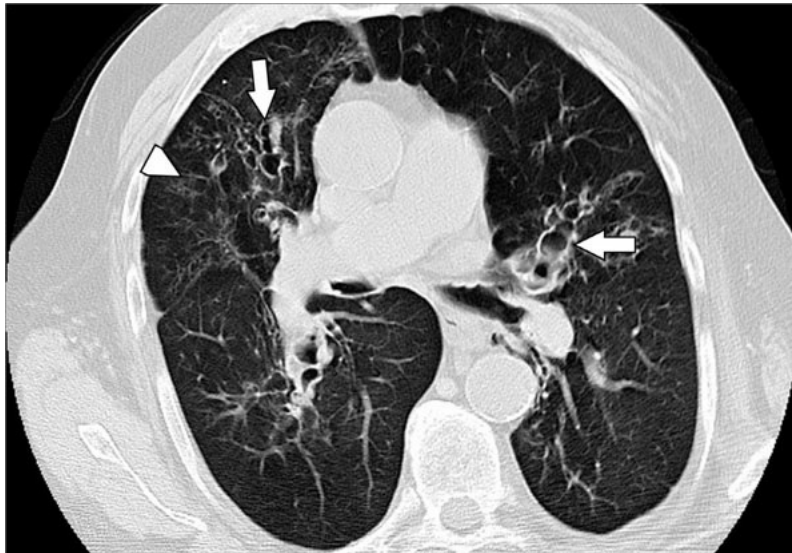
■ **FIGURE 11.3** Allergic bronchopulmonary aspergillosis in a 50-year-old man with asthma and eosinophilia. High-resolution computed tomography demonstrating extensive bilateral central bronchiectasis (*arrows*) and peripheral centrilobular nodules (*arrowhead*).

Hypersensitivity Pneumonitis

HP is a diffuse granulomatous interstitial lung disease caused by inhalation of airborne organic particulate matter (14,23). Causative factors are numerous and include bacteria, fungi, avian proteins, wood dusts, and chemicals. HP has been traditionally classified as manifesting in three phases: acute, subacute, and chronic. HRCT can be useful because patients with normal chest radiographs often have characteristic findings of centrilobular nodules and ground-glass opacities. These findings are most common in the middle-to-lower lung fields (23,24).

Acute HP occurs after intense exposure to antigens. HRCT findings of acute HP are those of acute pulmonary edema and include diffuse ground-glass opacities and thickening interlobular septa (23). The HRCT findings of subacute HP include diffuse or patchy ground-glass opacities and small focal areas of decreased attenuation on expiratory images caused by air trapping (23) (Fig. 11.4).

Chronic HP occurs after long-standing exposure to an offending antigen and can result in chronic pulmonary fibrosis. In chronic HP, the HRCT findings include multiple small nodular and irregular linear opacities with upper lung predominant fibrosis, including traction bronchiectasis, small areas of lobular lucency, and honeycombing. Mosaic attenuation on inspiratory and air trapping on expiratory images are common. The lung bases are typically spared (Fig.

11.5) (13,23,25).

Eosinophilic Lung Disease

Eosinophilic lung disease of unknown cause includes simple pulmonary eosinophilia (SPE), acute eosinophilic pneumonia (AEP), chronic eosinophilic pneumonia, eosinophilic granulomatosis with polyangiitis (EGPA) (formerly known Churg–Strauss syndrome), and idiopathic hypereosinophilic syndrome (HES) (26).
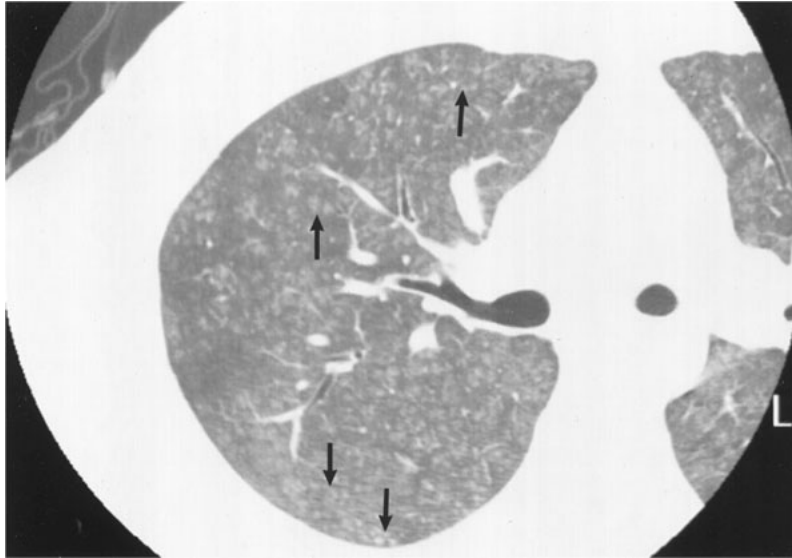
■ **FIGURE 11.4** Subacute hypersensitivity pneumonitis in a 30-year-old woman with acute dyspnea, hypoxemia, and chills after cleaning her attic. High-resolution computed tomography showing numerous centrilobular nodules (*arrows*). The radiologic and clinical findings resolved 5 days after initiating corticosteroid therapy.

SPE, also known as Loeffler syndrome, is characterized by transient and migrating opacities on chest radiography, increased peripheral eosinophilia, little or no pulmonary symptoms, and spontaneous resolution within 1 month. The HRCT findings consist of ground-glass opacity and consolidation involving mainly the peripheral regions of the upper and mid lung zones (26,27) (Fig. 11.6).

AEP is an idiopathic disease, with a male predominance, in which acute upper respiratory failure is accompanied by markedly elevated levels of eosinophilia in fluid recovered from bronchoalveolar lavage (26,28). Peripheral blood eosinophilia is rarely present. Patients with AEP present with fever and acute respiratory failure (26). Pleural effusions are a common feature associated with AEP. The CT findings include patchy ground-glass opacities, interlobular septal

thickening, and sometimes by pulmonary consolidation or nodules (Fig. 11.7). The radiographic differential diagnosis includes hydrostatic pulmonary edema, adult respiratory distress syndrome, and atypical viral or bacterial pneumonia.
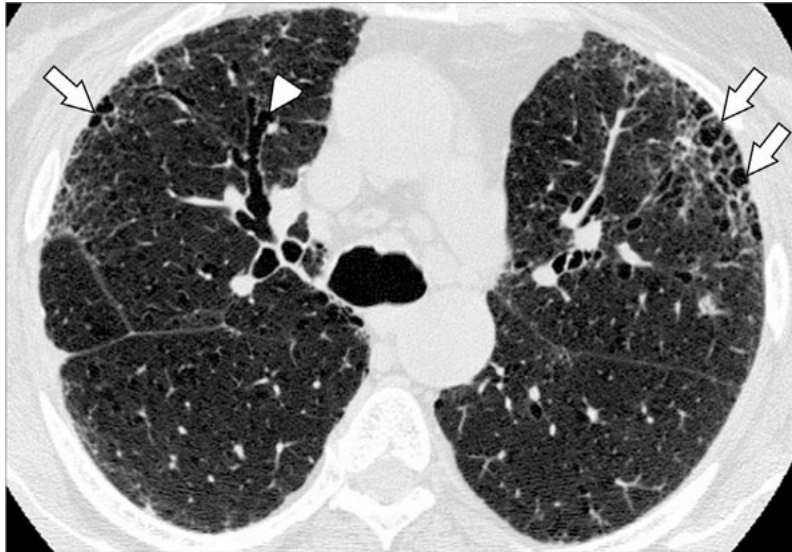
■ **FIGURE 11.5** Chronic hypersensitivity pneumonitis in a 52-year-old man with progressive dyspnea. Computed tomography showing traction bronchiectasis (*arrowhead*) and honeycombing (*arrows*).

■ **FIGURE 11.6** Simple pulmonary eosinophilia in a 19-year-old man with a cough and peripheral eosinophilia. High-resolution computed tomography showing peripheral small ground-glass opacities and centrilobular nodules in the upper lung zones (*arrowheads*).

Chronic eosinophilic pneumonia is an idiopathic condition histologically characterized by filling of the airspaces with eosinophils and macrophages and associated mild interstitial pneumonia. The patients are most often middle aged, and half of them have asthma. Patients usually present after several months of

cough, low-grade fever, weight loss, and dyspnea (26–28). On HRCT, a peripheral distribution of consolidation is often present, even when it is not apparent on chest radiographs (Fig. 11.8). The combination of peripheral unilateral or bilateral patchy consolidation and peripheral blood eosinophilia is virtually diagnostic for chronic eosinophilic pneumonia (29).
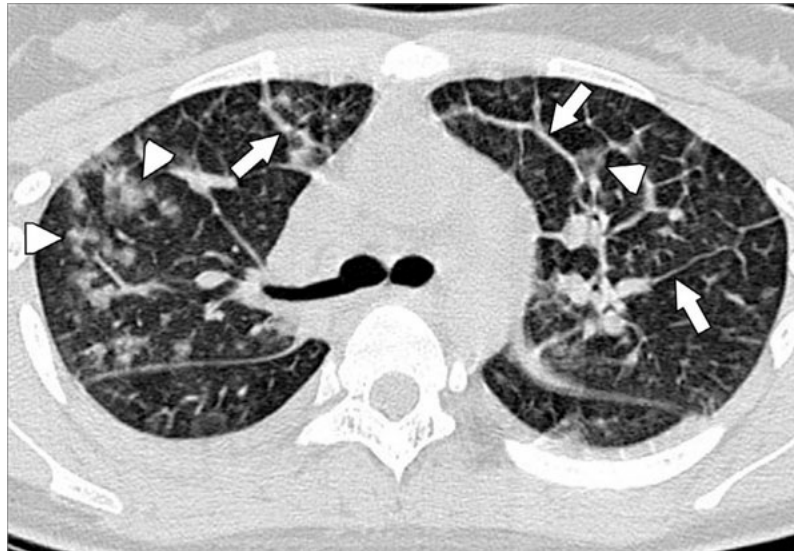
■ **FIGURE 11.7** Acute eosinophilic pneumonia in a 34-year-old woman with respiratory failure. High-resolution computed tomography demonstrating thickening of the interlobular septum (*arrows*) and ground-glass opacities (*arrowheads*).

Idiopathic HES is a rare and sometimes fatal disorder characterized by elevated blood eosinophil levels (>1,500 per μL) for more than 6 months. Cardiac involvement, including endocardial fibrosis and restrictive cardiomyopathy, is one of the major complications of this entity. Pulmonary involvement occurs in up to 40% of patients, and typically presents on radiography as interstitial, nonlobar opacities (26,30,31). The heart and central nervous system are typically involved. The radiographic manifestations of HES, although nonspecific, usually include diffuse pulmonary opacities related to severe cardiac failure.

EGPA (formerly known Churg–Strauss syndrome) is a rare allergic necrotizing vasculitis of unknown etiology (32–34). The syndrome is most commonly seen in patients 30 to 50 years of age and has no gender predilection. Patients are typically asthmatic and present with eosinophilia, fever, and multisystem vasculitis. Findings of chest radiography are often abnormal, but nonspecific and most often consist of patchy nonsegmental areas of consolidation with no zonal predominance. The areas of consolidation may have

peripheral distribution and are often transient. A pleural effusion is present in approximately 30% of patients, usually due to cardiac involvement or eosinophilic pleuritis (32). Up to 25% of patients with EGPA have few or no chest CT imaging abnormalities.
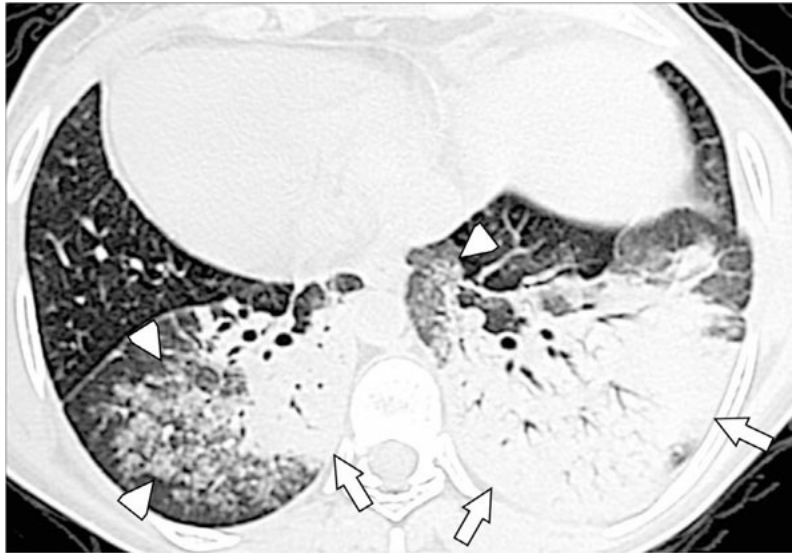
■ **FIGURE 11.8** Chronic eosinophilic pneumonia in a 60-year-old man. Transverse thin-section computed tomography demonstrating extensive areas of airspace consolidation (*arrows*) and ground-glass attenuation (*arrowhead*) involving the periphery of the lungs.
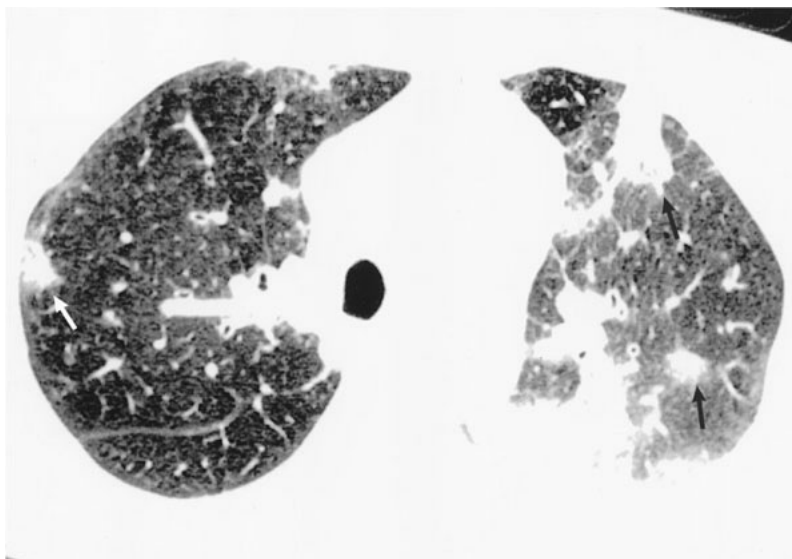
■ **FIGURE 11.9** Eosinophilic granulomatosis with polyangiitis. Computed tomography demonstrating irregular areas of consolidation (*arrows*) in a 57-year-old woman with previous episodes of eosinophilic pneumonia. An open lung biopsy revealed a necrotizing vasculitis.

Recent reports on the HRCT findings of EGPA have shown that they are

nonspecific. Findings include ground-glass opacities, consolidation, small centrilobular nodules, interlobular septal thickening, and bronchial wall thickening (Fig. 11.9). The ground-glass opacities and consolidation reflect the presence of chronic eosinophilic pneumonia (32).

Drug-Induced Lung Disease

Pulmonary drug hypersensitivity is increasingly being diagnosed as a cause of acute and chronic lung disease (35–37). Numerous agents, including cytotoxic and noncytotoxic drugs, have the potential to cause pulmonary disturbances. The clinical and radiologic manifestation of these drugs generally reflects the underlying histopathologic processes. These manifestations include diffuse alveolar damage, COP, eosinophilic pneumonia, and pulmonary hemorrhage (36,37).

Radiographic manifestation on CT includes diffuse areas of ground-glass opacity, diffuse areas of heterogeneous opacity, and, in the later stages, fibrosis, especially in a basilar distribution (Fig. 11.10). COP, which is commonly caused by cytotoxic drugs, appears on radiographs as heterogeneous and homogenous peripheral opacities and on CT as poorly defined nodules and consolidation (35,36).

The prevalence of drug-induced pulmonary hypersensitivity or toxicity is increasing, and more than 100 drugs are now known to cause injury. Because of its progressive nature, early recognition is important. The diagnosis of pulmonary drug hypersensitivity should be considered in any patient with drug therapy who presents with new progressive respiratory complaints.

■ **FIGURE 11.10** Drug-induced lung disease in a 49-year-old woman on

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chemotherapy for lymphoma. There are lower lobe peripheral poorly defined ground opacities (*arrows*). The lung biopsy showed cryptogenic organizing pneumonia.

IgG4-Related Disease

IgG4-RD is a chronic, relapsing-remitting inflammatory condition in which there is tissue infiltration with lymphocytes and IgG4-secreting plasma cells. The clinical symptoms of IgG4-RD may include cough, fever, dyspnea, and chest pain. The disease is more common in men over 50. While almost any organ can be involved, 14% of individuals have abnormal chest CTs. There is not a classic imaging finding, but it may mimic malignancy, presenting with pseudotumor. Other chest CT findings include organizing pneumonia, honeycombing fibrosis, or hilar and mediastinal adenopathy. Glucocorticoids are the mainstay of treatment (38).

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Chronic Rhinosinusitis: Role of Rhinoscopy and Surgery

RAKESH CHANDRA, DAVID B. CONLEY, AND ROBERT C. KERN

INTRODUCTION AND HISTORICAL PERSPECTIVE

Chronic rhinosinusitis (CRS) affects an estimated 31 million people in the United States. Management of this disorder, which accounts for approximately 16 million patient visits per year, has changed dramatically in the past 50 years. This is due to new insights into the pathophysiology of sinusitis, advances in rhinoscopy (nasal endoscopy), improved radiographic imaging, and availability of antibiotics (1). Technical advances in endoscopic instrumentation have defined a new era in the office diagnosis and surgical management of sinusitis, permitting an unprecedented level of precision. Understanding the indications as well as the technical limitations of diagnostic and therapeutic rhinoscopy is now essential for practitioners who manage CRS.

Hirschman performed the first fiberoptic nasal examination using a modified cystoscope in 1901 (2). Refinements in instrumentation after World War II allowed the development of smaller scopes that provided better illumination. In the early 1950s, investigators at Johns Hopkins University designed a series of endoscopes with relatively small-diameter, wide-field, high-contrast optics, and adequately bright illumination. At this time Messerklinger of Graz began to use this technology for systematic nasal airway evaluation. He reported that primary inflammatory processes in the lateral nasal wall, particularly in the middle meatus, result in secondary disease in the maxillary and frontal sinuses (2). This region, which represents a common drainage site for the maxillary, frontal, and anterior ethmoid sinuses, is termed the osteomeatal complex (OMC). Messerklinger found that small anatomic variations or even minimal inflammatory activity in this area could result in significant disease of the adjacent sinuses as a result of impaired ventilation and drainage. With this observation, he used endoscopes to develop a surgical approach to relieve the obstruction in such a way that normal sinus physiology was preserved. Specifically, he demonstrated that even limited surgical procedures directed

toward the OMC and the anterior ethmoid air cells could relieve obstruction of drainage from the frontal and maxillary sinuses. This philosophy was markedly different from the ablative sinus procedures advocated in the past, such as Caldwell-Luc, in that cilia and sinus mucosal function were preserved. Hence these procedures were termed functional endoscopic sinus surgery (FESS); Stammberger and Kennedy further refined these techniques in the 1980s.

ANATOMY AND PHYSIOLOGY OF THE SINONASAL TRACT

The frontal, maxillary, ethmoid, and sphenoid sinuses are formed early in development as evaginations of nasal respiratory mucosa into the facial bones. The ethmoid sinus develops into a labyrinth of 3 to 15 small air cells. In contrast, the other sinuses exist as a single bony cavity on each side of the facial skeleton. The ethmoid and maxillary sinuses are present at birth and can be imaged in infancy. The frontal sinuses begin to develop anatomically by 12 months and can be evaluated radiographically at 4 to 6 years. Sphenoid sinuses begin to develop by the age of 3, but cannot be imaged until a child is 9 or 10 years of age. The point at which mucosal outpouching occurs persists as the sinus ostium, through which the sinus drains (3).

Diagnostic rhinoscopy offers a wealth of information regarding the distribution of inflammatory foci within the sinonasal labyrinth and the associated anatomic variations that may impair physiologic sinus drainage. It is usually performed in an office setting with the aid of topical decongestants and topical anesthesia. It is essentially an extension of the physical examination that helps confirm the diagnosis, gain insight into the pathophysiologic factors at work, and guide medical or surgical therapy. The principles of diagnostic and therapeutic rhinoscopy are based on a firm understanding of the anatomy and physiology of the nose and sinuses (Fig. 12.1). The lateral nasal walls are each flanked by three turbinate bones, designated the superior, middle, and inferior turbinates. The region under each turbinate is known, respectively, as the superior, middle, and inferior meatus. The anatomy of the lateral nasal wall is of key importance for the understanding of sinonasal physiology and the principles of FESS, because the ostium of each sinus drains into an anatomically specific location. The frontal, maxillary, and anterior ethmoid sinuses drain on the lateral nasal wall in a region within the middle meatus, known as the OMC. This is an anatomically narrow space where, even minimal mucosal disease, can result in impairment of drainage from any of these sinuses.

The posterior ethmoid sinuses drain into the superior meatus but are often aerated via the middle meatus during FESS. The sphenoid sinus drains into a region known as the sphenoethmoidal recess, which lies at the junction of the sphenoid and ethmoid bones in the posterior superior nasal cavity. The nasolacrimal duct courses anteriorly to the maxillary sinus ostium and drains into the inferior meatus. The ethmoid bone is the most important component of the OMC and lateral nasal wall. It is a T-shaped structure, of which the horizontal portion forms the cribriform plate of the skull base. The vertical part forms most of the lateral nasal wall and consists of the superior and middle turbinates, as well as the ethmoid sinus labyrinth. Within the middle meatus, a sickle-shaped projection of the ethmoid bone, known as the uncinate process, forms a boundary of a recess called the infundibulum, into which the maxillary sinus drains (4).

A collection of anterior ethmoid air cells forms a bulla, which is suspended from the remainder of the ethmoid bone, and hangs just superiorly to the opening of the infundibulum into the meatus. The drainage tract for the frontal sinus courses inferiorly such that its ostium lies posterior and often just medial to the anterior most ethmoid air cell. Therefore, the main components of the OMC are the maxillary sinus ostium/infundibulum, the anterior ethmoid cells/bulla, and the frontal recess. The infundibulum and frontal recess exist as narrow clefts; thus, it is possible that even minimal inflammation of the adjacent ethmoidal mucosa can result in secondary obstruction of the maxillary and frontal sinuses, although it would be gross oversimplification to consider sinonasal inflammatory disease as a purely obstructive phenomenon.
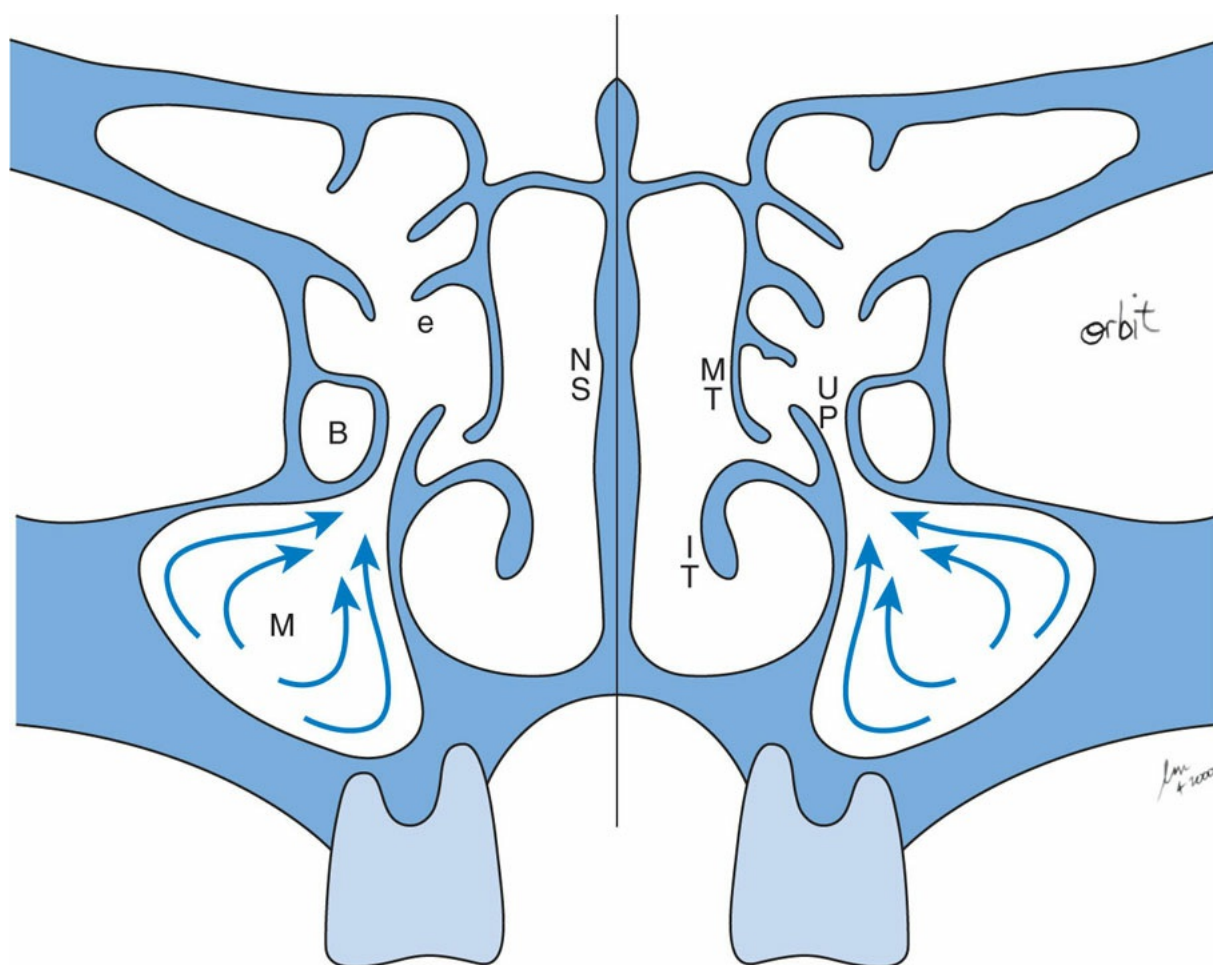
■ FIGURE 12.1 A schematic view of sinonasal anatomy in the coronal plane. The maxillary sinus (*M*), ethmoid labyrinth (*e*) and bulla (*B*), uncinate process (*UP*), nasal septum (*NS*), and middle (*MT*) and inferior (*IT*) turbinates are identified. The arrows demonstrate mucociliary clearance patterns in the maxillary sinuses. Cilia drive mucus toward the natural ostium.

The paranasal sinuses are lined by pseudostratified-ciliated columnar epithelium, over which lays a thin blanket of mucus. The cilia beat in a predetermined direction such that the mucous layer is directed toward the natural ostium and into the appropriate meatus of the nasal airway. This is the process by which microbial organisms and debris are cleared from the sinuses (4). This principle of mucociliary flow is analogous to the "mucociliary escalator" described for the tracheobronchial tree. The maxillary ostium and infundibulum are located superior and medial to the maxillary sinus cavity itself. Therefore, mucociliary clearance in the maxillary sinus must overcome the tendency for mucus to pool in dependent areas of the sinus. Successful FESS entails resection of obstructive inflammatory disease and enhancement of drainage via the natural ostia. Antrostomies placed in dependent portions of the sinus are less effective because they interfere with predetermined mucous clearance patterns. It is also

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important to preserve a layer of mucosal lining over post dissection cavities to maximize recovery of muciliary clearance postoperatively.

▪ PATHOPHYSIOLOGY OF CHRONIC RHINOSINUSITIS

Rhinosinusitis can be defined sinusitis as "inflammation of the mucosa of the nose and paranasal sinuses." *Rhinosinusitis*, rather than *sinusitis*, has been recommended as the more appropriate term, because sinus inflammation is often preceded by rhinitis and rarely occurs without coexisting rhinitis. Current guidelines also specify that there must be some objective evidence of mucosal inflammation, either by examination (usually endsoscopic) or radiology (usually computerized tomography [CT] scan) (5). Primary inflammation of the nasal membranes, specifically in the region of the OMC, results in impaired sinus drainage and bacterial superinfection, resulting in further inflammation (Fig. 12.2). In most patients, a variety of host and environmental factors serve to precipitate initial inflammatory changes. Host factors include systemic processes such as allergic and immunologic conditions, various genetic disorders (e.g., immotile cilia syndrome and cystic fibrosis [CF]), and metabolic/endocrine disorders. Host variations in sinonasal anatomy also occur, predisposing some to ostial obstruction with even minimal degrees of mucosal inflammation. Neoplasms of the nose and maxilla and nasal polyps (NPs) also may cause anatomic obstruction. Environmental factors play a vital role, including infectious agents, allergens, medications, trauma, and noxious fumes such as tobacco smoke (5). The pathophysiology of CRS can be influenced by sinonasal anatomy, infection, and allergic/immunologic disorders. Rhinoscopy can provide significant insight into the relative importance of these elements in each individual patient. The infectious, allergic, and immunologic elements of CRS are typically subjected to intense pharmacologic treatment. It should be noted that the specific immunologic factors that predispose a patient to CRS is an area of active investigation, and current evidence implicates many potential factors beyond IgE-mediated allergy. The disease process is better understood as a clinical syndrome caused by inflammatory etiologies, rather than as an infectious disease. Microorganisms, however, do play a significant role in the progression and exacerbation of the condition.
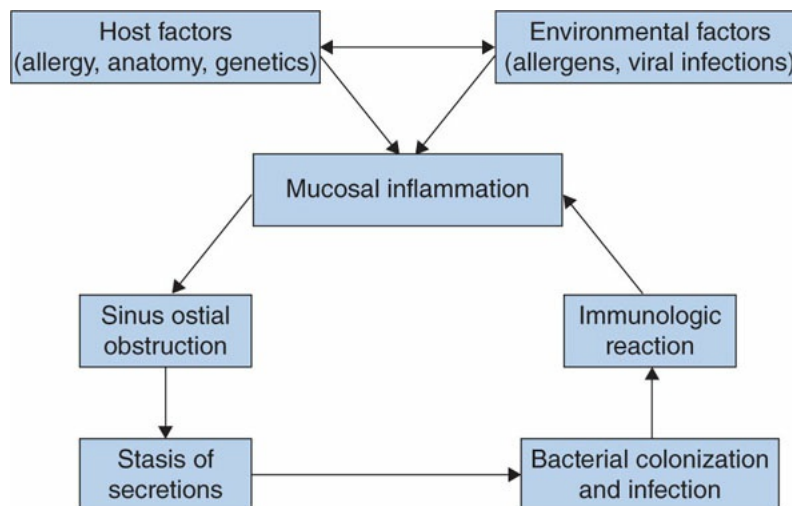
■ FIGURE 12.2 Pathophysiology of chronic rhinosinusitis—the cycle of inflammation.

Some of these underlying inflammatory factors may predispose the CRS patient to polyp growth, and prevailing thought suggests that polyp growth, at least in Western countries, is associated with a $CD4^+$ T helper 2 (TH2) cytokine profile (interleukins such as IL-4, IL-5, IL-13) and eosinophilic inflammation, while nonpolypoid CRS tends to exhibit $CD4^+$ mixed cytokine profiles including TH1, TH2, and TH17 and neutrophilic inflammation. This distinction may have significant therapeutic implications (6).

Anatomic Influences

Anatomic variations can contribute to the symptomatology in patients with CRS; these variations would include congenital, surgical, traumatic, or postinflammatory alterations in the normal structure. Common variations include septal deviations and spurs, and hypertrophic, pneumatized (concha bullosa), bent, or flattened turbinates. These entities create inherent anatomic narrowing of the bony channels through which mucus and air flow. When superimposed upon inflammatory edema of the overlying mucosa, these factors may initiate the cascade of events resulting in symptoms of nasal airway obstruction, and possibly limitation of mucocilliary flow. Anatomic obstruction may also be precipitated or exacerbated by mass effect from inflammatory polyps, and occasionally, true neoplasms are encountered.

Accessory sinus ostia may result in recirculation of mucus with diminished net mucociliary clearance. These factors may, theoretically, induce progression to CRS, although the exact relationship between various anatomic factors and the development of CRS has been difficult to demonstrate statistically. Diagnostic nasal endoscopy is an important modality to elucidate which of these entities (or

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combination thereof) may be implicated in any individual patient with CRS. A sample of commonly encountered endoscopic findings is illustrated in Fig. 12.3. Paranasal sinus imaging is reviewed in Chapter 10; it should be noted that CT scan of the sinuses and nasal endoscopy are complimentary diagnostic modalities, as illustrated in Fig. 12.4.

Infection

Rhinosinusitis often is preceded by an acute viral illness such as the common cold (5). This leads to mucosal swelling, obstruction of sinus outflow, stasis of secretions, and subsequent bacterial colonization and infection. From the acute phase, four possible courses are possible. These include resolution, progression with adverse sequelae such as orbital or intracranial infection, development of silent CRS, or the development of symptomatic CRS. In turn, CRS may undergo resolution, persistence, or the development of adverse sequelae, depending on the host and environmental variables at work (5). In the chronic persistent state, microbial colonization and infection lead to additional inflammation, further exacerbating the process.

With the development of symptomatic CRS, multiple bacteria usually are cultured, including anaerobes and β-lactamase–producing organisms (7,8). Some are apparently pathogens, whereas others are opportunistic, nonvirulent strains. Among pathogens, *Staphylococcus aureus* is most common, followed by Pseudomonas. Cultures obtained under rhinoscopic guidance or those obtained from tissue removed at surgery may help to guide appropriate antibiotic selection. Histopathologic studies of sinus mucosa taken from patients with CRS do not generally demonstrate bacterial tissue invasion. Current observations suggest that bacteria may exist upon sinonasal membranes in communities organized as biofilms with increased antibiotic resistance compared to free-floating planktonic bacterial forms (9). It is also known that normal sinonasal membranes harbor a local microbiome and that the diversity of these organisms is reduced in CRS patients with more severe clinical disease (10).

Allergic Rhinitis

The exact incidence of allergy in patients with CRS is unclear. It is reported that 38% to 67% of patients with CRS who require FESS have comorbid allergic rhinitis (9). This observation is true in children as well as adults. In susceptible individuals, provocation by airborne inhalant allergens triggers the release of mediators from mast cells that reside in the nasal mucosa. Immunoglobulin E (IgE)-mediated inflammation may hypothetically lead to mucosal edema and

osteomeatal obstruction, with secondary sinusitis. The early phase is primarily mediated by histamine and leukotrienes, whereas late-phase reactions result from cytokines and cellular responses. It should be noted that the prevalence of positive immediate skin testing is sometimes less than what would be expected intuitively, so that the overall impact of systemic IgE-mediated disease is still unclear. Nonallergic rhinitis, including vasomotor rhinitis, also can result in osteomeatal obstruction and secondary sinusitis.
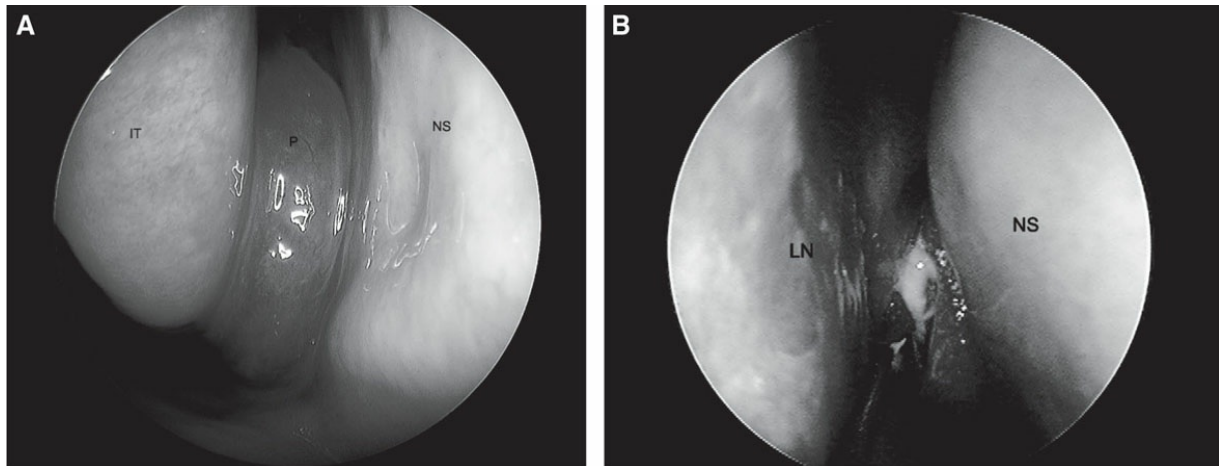
■ **FIGURE 12.3** Rhinoscopic diagnosis. **A:** View into right side of nose revealing a nasal polyp (*P*) occupying the nasal airway between the inferior turbinate (*IT*) and nasal septum (*NS*). **B:** View into right side of nose revealing polypoid change associated with pus in the middle meatus, which is the space between the middle turbinate (*MT*) and lateral nasal wall (*LN*) into which the frontal, maxillary, and anterior ethmoid sinuses drain. The nasal septum (*NS*) is also identified. As shown, a swab can be used for culture.
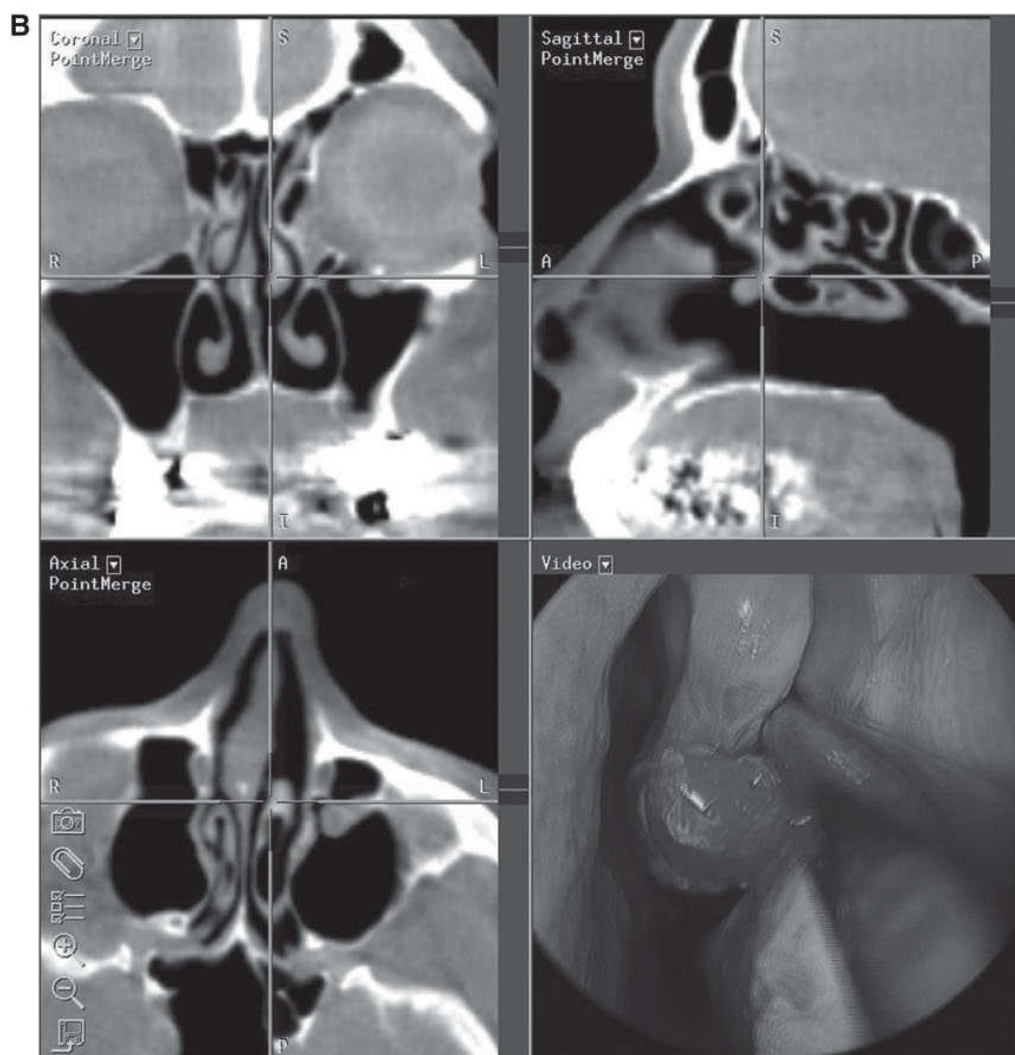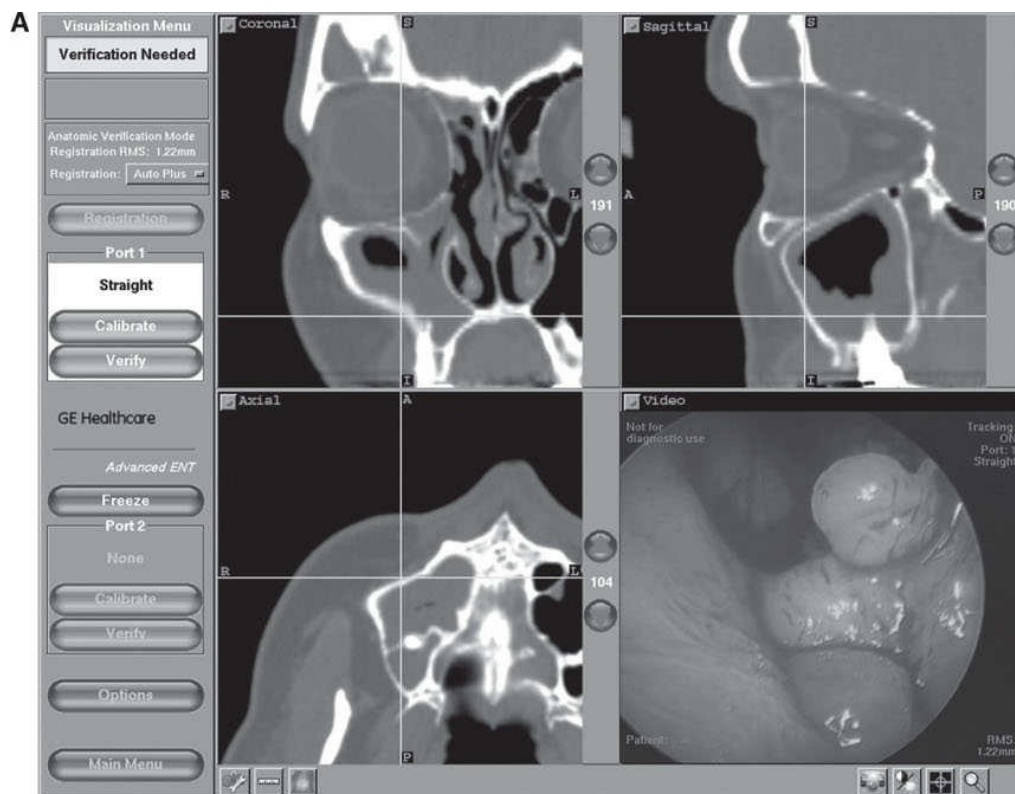
■ **FIGURE 12.4** Triplanar computed tomography (CT) reconstructions with endoscopic view. For each figure, the axial, coronal, and sagittal views are seen in the left lower, left upper, and right upper panels, respectively. Endoscopic correlation is seen in the right lower panel of each figure. **A:** These images reveal opacification within the right maxillary sinus. Endoscopic visualization demonstrates this to be a neoplasm, rather than a fluid collection or mucosal thickening, which may have similar radiologic appearances. This particular neoplasm was an inverting papilloma, which is the most common benign neoplasm of the sinonasal tract, but may have malignant potential. **B:** In this patient, although the endoscopic view clearly demonstrates a neoplasm (capillary hemangioma) pedicled to the head of the left middle turbinate, the CT images are relatively nondescript. Knowing that the pathology is present endoscopically, one is able to appreciate it on the sagittal image (crosshairs, right upper panel).

Nasal Polyps

The exact etiology of NPs is unknown, and likely mutifactorial. NP growth is associated with high-grade chronic sinonasal inflammation in *susceptible* individuals. Degranulated eosinophils often are present, and these cells are known to secrete IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GMC-SF), all of which are eosinophil growth factors (5). NPs also can be associated with specific disorders, such as aspirin-sensitive asthma and CF. The latter diagnosis should be excluded by chloride sweat test in any pediatric patient with NPs (2). The relationship of NPs to allergic rhinitis is uncertain (5). Because NPs observed on rhinoscopic examination may coexist with specific underlying disorders such as asthma, CF, or allergic fungal sinusitis (AFS; discussed further), their detection may indicate the need for further evaluation of these conditions.

Immune Deficiency

Immune deficiencies should be considered in patients with CRS or recurrent acute rhinosinusitis (RARS). Some individuals with RARS or CRS may have a humoral immune deficiency. The most common is IgA deficiency, but IgG deficiency also may occur. Antibody defects predispose the patient to infection with encapsulated gram-positive and some gram-negative organisms. Recent attention has been given to specific antibody deficiency whereby patients are unable to generate a sufficient antibody response to polysaccharide antigens. This is assessed by baseline titers to 14 pneumococcal capsular polysaccharide antigens. Generally, patients must exhibit protective levels to 7/14 to be

considered immunocompetent in this area, and some (25% in the authors' practice) are still deficient despite vaccination (11).

Antibody deficiencies contrast with T-cell deficiencies, which render the patient more susceptible to viral, fungal, and protozoal infections. Terminal complement component defects are associated with Neisserial infections. Thus, the particular type of immune deficiency dictates the nature of the infectious organisms (9). These observations are particularly important in this era of widespread acquired immunodeficiency in which sinusitis can be more atypical than in the general population. Subjects with HIV/AIDS can have CRS with normal to elevated total IgE concentration but absent immunity to *S. pneumonia*. Rhinoscopically directed cultures may be useful in the diagnosis and management of atypical infections.

Allergic Fungal Sinusitis

AFS is a pathologic entity distinct from invasive fungal sinusitis. The latter is a fulminant infectious process with tissue invasion; chronicity is rare. In AFS, however, chronic hypersensitivity to dematiaceous fungi is associated with nasal polyposis, obstruction, and multiple sinus involvement. Initially, the immunologic processes at work in AFS were thought to involve type I, type III, and/or type IVa_2 hypersensitivity, which are also observed in allergic bronchopulmonary aspergillosis (12). Recent studies, however, have suggested that AFS is predominantly mediated by eosinophils and that non-IgE-mediated mechanisms of TH2 stimulation (especially IL-5 production) are most important (13).

The hallmark rhinoscopic finding in classic AFS is thick, tenacious "peanut butter"–like inspissated mucus within one or more paranasal sinuses. Histologic examination of this "allergic mucin" reveals embedded eosinophils, Charcot–Leydin crystals (eosinophil breakdown products), and extramucosal fungal hyphae. Although bone destruction and expansion may occur, the disease most often follows a slow, progressive course and thus represents a unique form of CRS. In fact, classic AFS may occur in up to 7% of patients with CRS. The incidence of nasal polyposis in this disorder is high and, by some definitions, is required for diagnosis. NPs, in combination with allergic mucin, often lead to secondary osteomeatal obstruction. Fungal-specific IgE can be detected by immediate skin testing or *in vitro* assay.

Superantigens

One area of active investigation involves the role of immunologic response to *S. aureus* enterotoxins in the pathophysiology of CRS. In addition to causing ciliostasis (14), these proteins appear to have the ability to function as "superantigens," in that they are able to crosslink the class II major histocompatability complex of antigen presenting cells and the beta chain variable region of the T-cell receptor, which results in activation of large numbers of T cells (6). This is reported to result in vigorous production of TH2 cytokines, including IL-4, IL-5, IL-13, and eotaxin with concomitant NP formation. These data underscore the principle that although CRS is not primarily an infectious disease, microorganisms may have a significant role in the pathophysiology, in susceptible individuals.

Innate Immunity

All of the aforementioned etiologic processes rely on susceptibility of the patient to infection, antigen exposure, and/or immunologic responsiveness. In this vein, recent studies also have examined the role of innate immune defenses of sinonasal epithelial cells in the development of CRS (15). It appears that airways epithelial cells themselves are immunologically active participants that are able to respond to microbial exposure. Notable innate defenses appear to involve Toll-like receptors that mediate proinflammatory responses to microbes and surfactant proteins.

Any combination of the previously discussed inflammatory and anatomic factors can result in the histopathologic picture of CRS, a proliferative process associated with fibrosis of the lamina propria and an inflammatory infiltrate of eosinophils, lymphocytes, and plasma cells. Chronic mucosal inflammation also may induce osteitic changes of the ethmoid bone (5). Although the precipitating and potentiating causes for CRS are multifactorial, the common outcome is a cycle by which ostial obstruction leads to stasis of secretions, microbial colonization, and further inflammatory changes and NP formation in susceptible individuals.

THE DIAGNOSIS OF CHRONIC RHINOSINUSITIS

The presence of two or more major factors or one major and two minor factors (Table 12.1) is considered a "strong history for rhinosinusitis"; however, some objective assessment of disease must be observed (5). Nasal purulence alone is considered diagnostic of sinusitis, and rhinoscopic examination clearly can document this physical sign. A stream of purulent mucus (Fig. 12.3B) may be apparent draining from beneath the middle turbinate, and endoscopically directed

cultures of this drainage may be of particular value in guiding antibiotic therapy. The findings of polyps, polypoid changes, or mucosal inflammation are also suggestive of CRS. The current guidelines suggest that one or more of these physical manifestations of CRS should be present to satisfy the diagnosis. Endoscopy is thus critical in the evaluation of patients who meet the symptomatic criteria of CRS. This is often confirmed by CT scan that may reveal mucosal thickening, sinus opacification, and/or air fluid level.

Classification of sinusitis as acute (<12 weeks), recurrent acute, or chronic is dependent on temporal patterns (5). A diagnosis of CRS requires that signs and symptoms persist for longer than 12 weeks. Patients also may have acute exacerbations of CRS in which they experience worsening of the chronic baseline signs and symptoms or the development of new ones. These patients do not have complete resolution of symptoms between exacerbations, in contrast to those with recurrent acute sinusitis. Given the multifactorial nature of its etiology and the diversity of signs and symptoms, CRS can be considered a syndrome. Generally, CRS is the most common indication for FESS; the goal of surgery is to remove symptomatic anatomic obstruction that has failed to respond to aggressive medical therapy. The resulting improvement in sinus ventilation and drainage often promotes relief of inflammation and resolution of symptoms.

TABLE 12.1 MAJOR AND MINOR FACTORS IN THE DIAGNOSIS OF RHINOSINUSITIS

MAJOR FACTORS	MINOR FACTORS
Facial pain/pressure	Headache
Facial congestion/fullness	Fever (all nonacute forms of sinusitis)
Nasal obstruction/blockage	Halitosis
Nasal discharge/purulence	Fatigue
Discolored post nasal drip	Dental pain
Hyposmia/anosmia	Cough

Purulence in nasal cavity	Ear pain/pressure/fullness
Fever (acute sinusitis only)	

Rhinoscopic Diagnosis

Nasal endoscopy is an extension of the physical examination that offers significant insight into the pathologic factors at work in CRS. For centuries, the standard of diagnosis was visualization anteriorly using a nasal speculum and posteriorly using an angled mirror placed in the pharynx. Rhinoscopy using a rigid fiberoptic telescope, however, is considered more accurate and thorough, and can be performed at a reasonable cost. Several scopes are available to provide visualization with different angles of deflection (Fig. 12.5). The zero-degree telescope, e.g., gives a direct and magnified view of structures directly in front of the tip of the scope. In contrast, the 30° scope evaluates structures located at a 30° inclination from the long axis of the instrument in the direction of the bevel. Flexible endoscopy is preferable for patient comfort. Prior to the performance of endoscopy, the nose is topically decongested and anesthetized with a combination of phenylephrine or oxymetazoline (for decongestion), and lidocaine or pontocaine (for anesthesia). These are administered in aerosolized spray form. Decongestion temporarily shrinks the inflamed nasal mucosa, allowing the scope greater access to critical areas. The topical anesthesia improves patient comfort and compliance during the examination. Most endoscopists examine the key areas in a systematic sequence. Regardless of the order, attempts should be made to visualize the following: nasal septum, inferior turbinate and meatus, middle turbinate and meatus, superior meatus, sphenoethmoidal recess, and the presence of accessory ostia.

In examining patients who have a history consistent with sinusitis, specific pathology that is not evident by a speculum examination may be detected by fiberoptic rhinoscopy. These include middle meatal polyps, pus, turbinate pathology, alterations in mucous viscosity, and synechiae (scar bands). In AFS, allergic mucin may be apparent in addition to NPs. Anatomic abnormalities of the septum, turbinates, or meatus are noted. These may contribute to the development of CRS by causing ostial obstruction. In the absence of symptoms and mucosal inflammatory changes, findings such as a deviated septum or a

concha bullosa are considered incidental. In each particular case, the surgeon must assess the degree of pathology and the contribution of anatomic abnormalities to that pathology. Those factors that appear to affect sinus drainage can then be addressed.

An additional role of diagnostic rhinoscopy is to rule out the presence of benign or malignant neoplasms of the nose and paranasal sinuses. These pathologies can cause anatomic obstruction of sinus drainage and thus produce symptoms of CRS. Suspicious lesions observed rhinoscopically can be examined via biopsy with endoscopic guidance, often in the office setting. The differential diagnosis of sinonasal masses includes benign and malignant salivary gland tumors, inverting papilloma, and sinonasal carcinoma. These entities are relatively rare; their discussion is beyond the scope of this chapter. It is nonetheless important to note that rhinoscopic examination may reveal pathology that may not be suspected on the initial history and physical examination in a patient with symptoms of CRS.
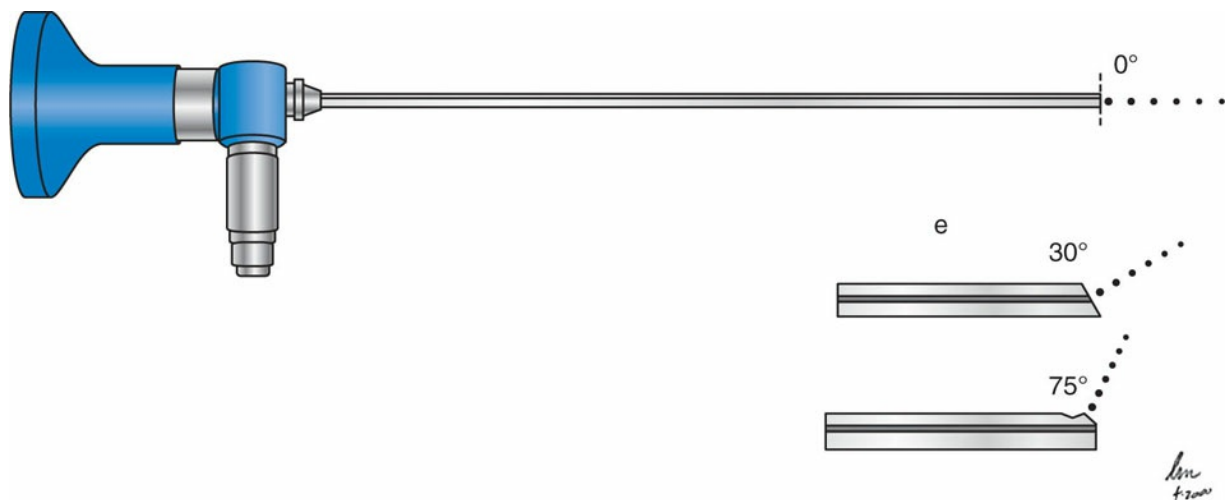
■ **FIGURE 12.5** Representative rhinoscopes. Note the variation in angle of view between the 0°, 30°, and 75° tips.

Radiologic Diagnosis

Imaging has become a critical element in the diagnosis of sinusitis, the determination of the extent of inflammatory disease, and the evaluation of sinonasal anatomy; it is discussed in detail in Chapter 10. By the time FESS was introduced in the United States in 1984, CT scan had become the radiologic modality of choice for diagnosis of sinusitis. Prior to this, imaging studies for sinusitis were conventional radiography and polytomography. CT scan has continued to be the gold standard, and its advantages continue to grow. At many institutions the cost of a screening coronal sinus CT scan limited sinus series is

comparable with that of a plain film sinus series and provides far more clarity of bony detail. With improved technology, CT scan is being performed more quickly and with lower radiation doses. Therefore, CT stands as a cost-effective, efficient, safe, and informative modality. CT scan is also being used with ever-increasing frequency for image-guided surgery. In this practice, CT data are digitized into a computer system that allows the surgeon to correlate endoscopic anatomic points with those on the digitized CT scan (Fig. 12.4) (16).

Magnetic resonance imaging (MRI) has become more widespread, accessible, and affordable during recent years. Its utility in sinonasal imaging, however, is limited secondary to its inability to display fine bony detail. MRI, nonetheless, is useful in the detection of disease extension into adjacent compartments such as the brain and orbit. Compared with CT, MRI may better distinguish neoplastic from inflammatory processes and may more accurately distinguish fungal disease from other inflammatory conditions (16).

CT accurately demonstrates mucosal thickening within the sinus cavities and deep in the OMC (16), the degree of bony thickening, and the presence of NPs, air-fluid levels, or sinus opacification (Fig. 12.4). The number and location of the involved sinuses also can be determined. In fact, several staging systems have been developed attempting to grade the severity of sinusitis based on these variables (17). The presence of bony anatomic variations that may contribute to the pathology of CRS also can be detected. The CT scan should be viewed as an adjunct to rhinoscopy rather than a replacement for this procedure. Most importantly, the CT scan confirms and documents osteomeatal obstruction. A patient with sinusitis symptoms despite aggressive medical therapy who has sinus outflow obstruction on a CT scan is a typical candidate for FESS.

FUNCTIONAL ENDOSCOPIC SINUS SURGERY

Indications

Initial treatment for CRS is medical. This may include any combination, depending on underlying causes, of topical steroid nasal sprays, oral steroids, antihistamines, decongestants, antibiotics, and nasal saline irrigations, which is discussed in Chapter 27. Identification and avoidance of causative allergens are also indicated. Medical therapy usually should be the first-line treatment in uncomplicated cases, with a course of a broad spectrum antibiotic, generally recommended for a minimum duration of 3 weeks. It should be noted that this recommendation is based upon consensus opinion rather than controlled scientific evidence. Surgical indications include chronic or recurrent acute

pansinusitis, frank nasal polyposis, mucocele, pending orbital or cranial complications, mycotic infections, debilitating headache, and olfactory dysfunction (18,19). The most common clinical setting for FESS is persistent rhinosinusitis symptoms despite an extended course of comprehensive medical therapy coupled with a CT scan demonstrating inflammatory disease. There are some data to suggest that FESS can reduce significantly both the number of infections requiring antibiotics and the severity of facial pain or headache in patients with recurrent acute sinusitis who have normal CT scans; this subset of patients is thought to have reversible nasal mucosal disease (20). Although FESS may have a role in the management of carefully selected symptomatic patients with normal CT scans, and presumptive *recurrent acute* rather than CRS, the exact indications for surgery in this patient population are unclear.

In cases of extensive polyp disease, surgery is not curative but does improve symptoms and efficacy of medical therapy. These patients often require revision surgery and are committed to long-term topical (and occasionally oral) steroid therapy. Thus, surgery is considered palliative in these cases because it cannot address the underlying pathophysiologic process (18), although it can dramatically improve the patient's quality of life. Uncomplicated pediatric CRS that is refractory to medical management is only considered a relative indication for FESS. In these cases, adenoidectomy is first-line surgical therapy if the adenoid pad is enlarged (21).

Preoperative Imaging

The importance of preoperative CT scanning cannot be overstated. This is crucial prior to the performance of FESS, not only for diagnostic purposes, but to demonstrate the relationships between the paranasal sinuses and critical surrounding structures, such as the brain, orbit, and carotid artery. The ethmoid sinus system forms the skull base, and the frontal, maxillary, and ethmoid sinuses surround the orbit (Fig. 12.1). Anatomic details vary from patient to patient and must be correlated with endoscopic data for the safe performance of FESS (16). It is important to remember, however, that the CT scan represents only one point in time, and thus does not always predict the extent of inflammatory disease that will be encountered at surgery.

Unless orbital or intracranial complications are pending, it is preferable to avoid operating in the setting of acute symptom exacerbations in order to minimize the risks of complications such as perioperative bleeding. Also, the use of aspirin and other nonsteroidal anti-inflammatory drugs is discouraged within 2

weeks of surgery. The usual preoperative studies, including laboratory studies, chest radiography, electrocardiography, and cardiac/pulmonary consultation, are obtained as indicated. Finally, the potential complications of FESS are discussed with the patient, and informed consent is obtained.

Intraoperative Procedure

After the administration of general anesthesia or sedation, topical anesthetics and vasoconstrictors are applied. Under endoscopic visualization, lidocaine with epinephrine can be injected submucosally at key points. This provides vasoconstriction and obviates the need for deeper planes of systemic anesthesia.

When it is deemed that septal deviation contributes to ostial obstruction, a septoplasty (straightening of the septum) is performed. In some instances, septoplasty is necessary to allow surgical access (passage of the endoscope and forceps) to posterior areas in the nasal cavity. Also, the middle turbinate may be collapsed onto the lateral nasal wall and must be displaced medially, or even partially resected, for access to the OMC. The same situation can exist if the turbinate is hypertrophic or pneumatized concha bullosa.

Any NPs are removed, and the uncinate process is resected to open the infundibulum. Pus and/or allergic mucin are suctioned or irrigated from the cavities. Removal of diseased tissue almost always can be accomplished via endonasal endoscopic approaches, although adjunctive external incisions are sometimes indicated. Representative steps are depicted in Fig. 12.6. The goal of FESS is to resect the inflamed ethmoidal tissue and to reestablish ventilation in the diseased larger sinuses by enlargement of their natural ostia, thus breaking the cycle of inflammation described earlier. Bony and mucosal septations between ethmoid cells are removed to create an unobstructed cavity. The ostia of the maxillary, sphenoid, and/or frontal sinuses can be enlarged, and NPs or inspissated mucous can be extracted. Subsequent mucous membrane recovery reestablishes mucociliary clearance via the newly enlarged physiologic ostia (Fig. 12.7). Any purulent material encountered intraoperatively may be sent for culture to guide future antibiotic therapy, and resected tissue is sent to pathology for histologic evaluation.

The operation may be performed unilaterally or bilaterally, and the extent of dissection is tailored according to the extent of disease severity. Although earlier reports suggested that each side could be dissected in as little as 5 to 20 minutes, recent practice has elucidated the importance of meticulously maintaining the mucosal lining of the final post dissection cavities, often prolonging the

procedure. In children, the frontal and sphenoid sinuses are often underdeveloped; therefore, only limited anterior ethmoid and maxillary work is generally necessary. As a consequence of the smaller anatomy, pediatric FESS requires a more meticulous technique (22). The last decade has also witnessed proliferation of balloon dilational technology where natural outflow tracts for the maxillary, frontal, and sphenoid sinuses can be enlarged without necessarily removing the inflammatory disease in selected patients. These techniques may also be incorporated into traditional FESS, as adjunctive maneuvers, to help localize and enlarge sinus ostia prior to disease (e.g., polyp) resection.

Other recent trends include the use of bio-absorbable steroid-eluting stents following FESS dissection (23). Some studies have suggested that these are associated with reduction of recurrent polyposis, development of scar tissue requiring lysis, and need for oral steroids at one month postop. However, additional randomized controlled trials are necessary to elucidate long-term outcomes and which subsets of patients are most likely to benefit. Overall, although the value of these stents is clearly beyond experimental at the time of this writing, this is an area where significant innovation is anticipated.
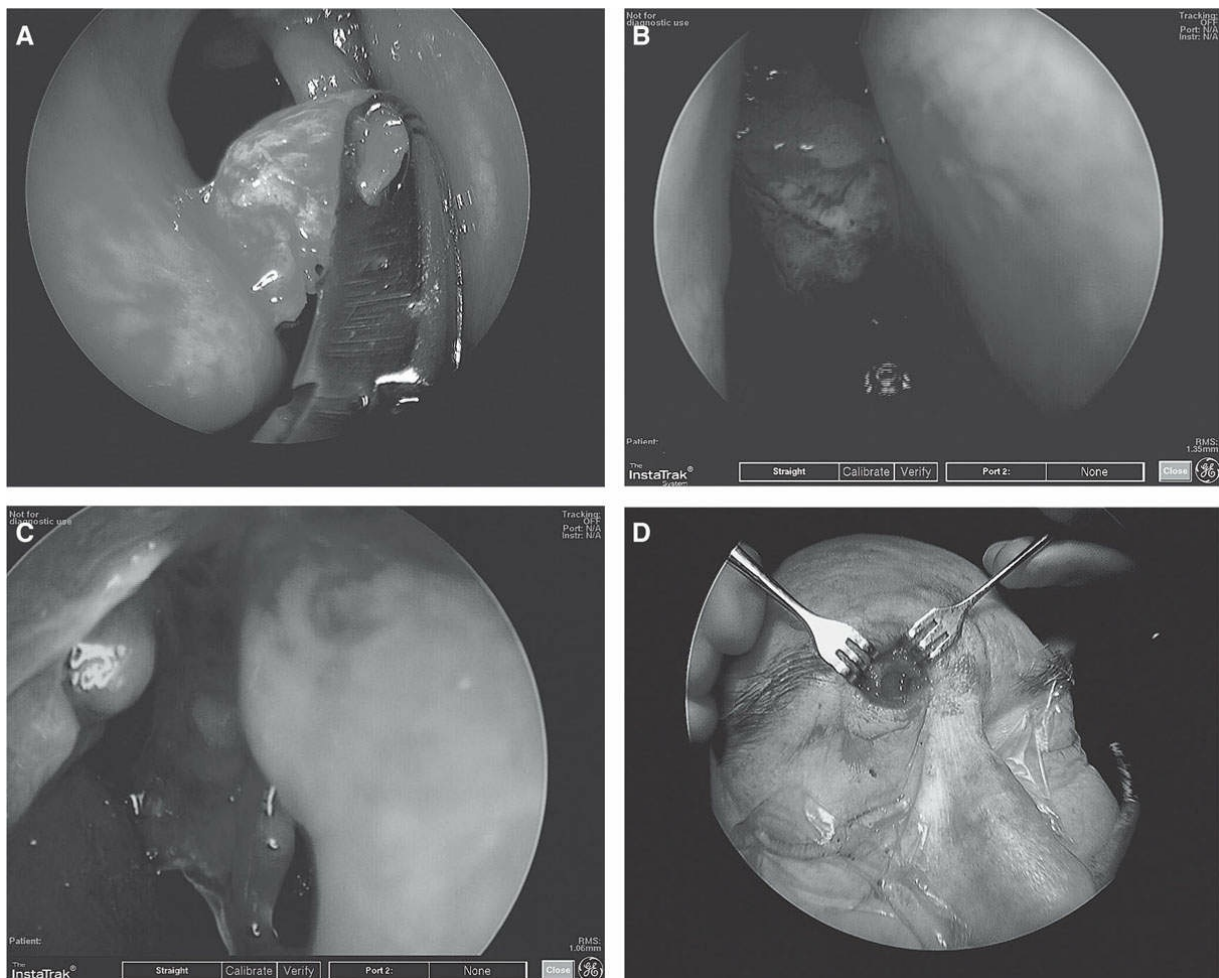
FIGURE 12.6 Surgical instrumentation. **A:** Standard endoscopic forceps removing the left uncinate process. **B:** The microdebrider has suction and an oscillating cutting window at its tip. This instrument is ideal for polyp resection. **C:** Allergic fungal mucin encountered in the ethmoid cavity, with associated polypoid changes of the adjacent mucosa. This mucin will have a "peanut butter-like" consistency. **D:** Although sinus surgery is performed via endonasal endoscopic approaches in the vast majority of cases, external approaches are occasionally necessary to manage tumor or pending complications, such as orbital extension.

Postoperative Management

The patient may be discharged on the evening of surgery or observed overnight in the hospital. Antibiotic prophylaxis against toxic shock syndrome is necessary if nasal tampons are placed. Approximately 1 to 7 days after the operation, any tampons are removed and the postsurgical cavity is debrided of crusted secretions and blood under endoscopic guidance in the office. The role for sinonasal endoscopy therefore extends into the postoperative period. This debridement is repeated two or three more times during the first postoperative weeks, at which time the ethmoid cavity begins to mucosalize. The larger sinuses may require up to 6 weeks to heal, particularly in the setting of nasal polyposis (20,24). During recovery, topical nasal steroid sprays and saline sprays are often recommended. Patients are told to refrain from exercise and heavy lifting for 1 to 2 weeks postoperatively. After the initial series of debridements, further office visits for diagnostic rhinoscopy are performed at 3-month intervals (18).

Complications

The incidence of major complications from FESS ranges from 0% to 5%. Examples include cerebrospinal fluid (CSF) leak, nasolacrimal duct injury, hemorrhage requiring transfusion, blindness, and meningitis. Minor complications occur in 4% to 29% of cases and include synechiae, orbital entry, ecchymosis, orbital emphysema, and minor hemorrhage (25).

Synechiae are considered the most common complication overall and occur in up to 8% of patients. Of the affected patients, however, only 15% experience persisting symptoms as a result. These scar bands are usually found between the anterior portion of the middle turbinate and the lateral nasal wall, where they may cause functional stenosis of the middle meatus (20).
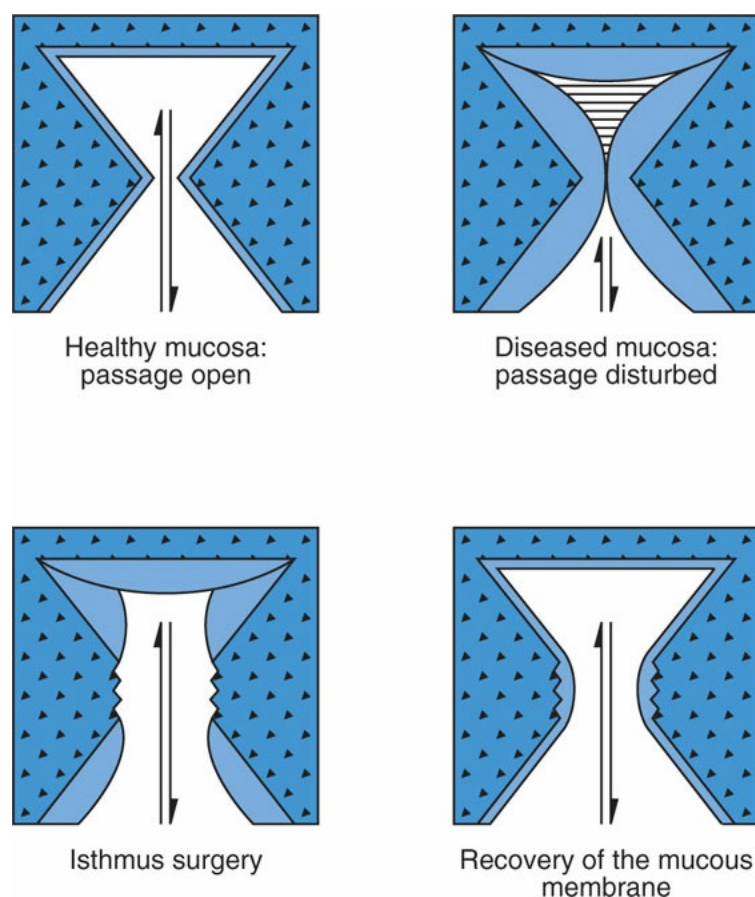
■ FIGURE 12.7 Principle of functional endoscopic sinus surgery. After mucosal recovery, the result is a dilated natural ostium. (Reprinted from Wigand ME. *Endoscopic Surgery of the Paranasal Sinuses and Anterior Skull Base*. New York: Thieme; 1990; with permission.)

The incidence and severity of postoperative hemorrhage is reported to be increased in patients with acquired immunodeficiency syndrome and diffuse polyp disease, and in revision cases (20). Fortunately, intraoperative bleeding is usually controlled by local anesthetic or cautery and is seldom a problem. If bleeding impairs the surgeon's visualization, however, the procedure is terminated and the nose is packed. Generally, the average blood loss is less than 30 mL (20).

Orbital penetration occurs in 2% to 4% of cases, and in up to one-third of these cases there is also orbital emphysema. Blindness, fortunately, is rare, with an incidence as low as zero in several large series (19,20,25). CSF leakage may occur in up to 1.4% of cases (20), but in skilled hands, the incidence is lower than 0.1% in large series (20,24).

Prognosis

Overall, FESS is considered successful in 80% to 90% of cases after at least 2

years of follow-up (19,20). However, FESS is generally a palliative procedure in patients with diffuse polyp disease. One study reported that 55% of patients with preoperative NPs had persistent disease at long-term follow-up, average 3 years and 5 months (19). Nonetheless, it is clear that surgery has a definite role in these patients because over half of the patients were asymptomatic or significantly improved and none was worse. As may be expected, however, results were better in those with a lesser degree of preoperative NP disease (19).

Most experts believe there is a link between asthma and CRS, although the details of this relationship are unclear. Recent studies have reported that CRS patients with steroid-dependent asthma have dramatically reduced steroid requirements after FESS. The patients studied required an average of 1,300 mg less prednisone and 21 fewer days of treatment in the year after FESS compared with the year before (63 days versus 84 days) (26). Antibiotic use also was significantly reduced after FESS in these patients (25). Other trials have reported similar results. For example, in one study 40% of patients with asthma were able to discontinue steroids after intranasal polypectomy (27), and another group demonstrated that 90% of patients had improvement in asthma symptoms 6.5 years after FESS (28). In some cases, it has been speculated that the removal of bacterial biofilms during FESS may be partially responsible for patient improvement (29).

Ongoing investigation continues to explore the impact of FESS upon both general and disease-specific quality of life, sleep, workplace productivity, social/emotional well-being, and comorbid conditions. A recent multi-institutional study (30) analyzed patients among three cohorts: surgical intervention ($n = 65$), continued medical therapy alone ($n = 33$), or crossover of medically treated patients later electing surgery ($n = 17$). All patients were deemed surgical candidates, and offered FESS, but selection of treatment course was patient-driven. At 1-year follow-up, a greater frequency of improvement was found in the surgical versus the medical cohort with respect to several domains assessed by the rhinosinusitis disability index and chronic sinusitis symptomatology using validated survey instruments. Quality of life in the crossover arm was stagnant or slightly worsening, until the patient proceeded with surgery after which improvement was observed. Additional investigations by these and other authors have sought to determine factors which distinguish those who benefit most from surgery as related to patient demographics, disease phenotype, and comorbidities.

SUMMARY

CRS is a clinical syndrome associated with persistent, symptomatic inflammatory changes in the sinonasal mucosa. Rhinoscopy and sinus CT scans may demonstrate associated mucus outflow obstruction. The role of surgery is primarily reserved for the management of patients who fail medical therapy necessitating reversal of congenital and acquired sinus outflow obstruction and restoration of normal nasal physiology. Technologic advances in rhinoscopic instrumentation have improved the accuracy of the office diagnosis and the precision of the surgery. Prior to the advent of surgical telescopes, sinus procedures were destructive in nature, with permanent alteration of sinus physiology. The precision afforded by the current technology permits less invasive surgical intervention in the attempt to restore normal function to sinus cavities and to optimize the efficacy of medical therapies.

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Principles of Immunologic Management of Allergic Diseases Due to Extrinsic Antigens

LESLIE C. GRAMMER AND KATHLEEN E. HARRIS

INTRODUCTION

Allergic diseases are generally treated using three principal modalities: avoidance of allergens, pharmacologic therapy, and immunotherapy. Pharmacologic treatment is discussed in the chapters relating to specific allergic diseases and in the chapters devoted to specific pharmacologic drug classes. The immunologic interventions, avoidance of allergens, and administration of immunotherapy are the subjects of this chapter.

ALLERGEN EXPOSURE RISK

Sensitization and exposure to a variety of allergens have been associated with asthma among children and young adults in numerous studies, with odds ratios ranging from 3 to 19 (1). Allergen importance varies with geographic location. Sensitization to house dust mite as a risk factor for asthma has been reported in humid climates such as Georgia, Virginia, Australia, New Zealand, and the United Kingdom (2). In drier climates, such as Sweden (3) and New Mexico (4), sensitization to cat and dog dander has been associated with increased risk for asthma. Children in the inner city who become sensitized to cockroach (5) or rodent (6) allergens are at increased risk for asthma. All of these studies suggest that avoidance of sensitization might reduce the predisposition to asthma. Unfortunately, avoidance is not always simple. For instance, even if cockroaches and pets can be avoided at home, school dust may have very high levels of these allergens (5,7), resulting in sensitization.

AVOIDANCE OF ANTIGENS

Allergic diseases result from antigen–antibody interaction that subsequently results in release of mediators and cytokines that affect target organs. If exposure

to the antigen or allergen can be avoided, no antigen–antibody interaction takes place, and, thus, there are no allergic disease manifestations. Consequently, the first tenet of allergic management is to remove the allergen if possible. In the case of certain allergens, removal can be accomplished fairly well. For instance, an individual who is sensitive to cat or dog dander or other animal protein should not have the animal in the home if complete control of symptoms is the goal of management. Individualized, comprehensive, home-based environmental interventions to reduce exposure to indoor allergens have been reported to result in reduced asthma-associated morbidity.

House Dust Mite

In the case of house dust mite allergy, complete avoidance is not possible in most climates, but the degree of exposure to this allergen can be diminished. House dust mite control measures that have been reviewed in a recent practice parameter are listed in Table 13.1 (8).

The effectiveness of controlling mite allergens in beds by using encasings is well established (9), but, as an isolated measure, it is not likely to be effective. Washing linens weekly is advised, but high temperature is not necessary. Home hot water should be kept below 120°F to minimize scalding risk (8). It is well recognized that carpet is a reservoir for mites; polished floors are preferable, especially in the bedroom (10). Several studies have reported the association between indoor humidity and dust mite allergen levels. For this reason, the relative humidity in the home should be kept below 50%.

Relative to ionizers or filtration devices, including high-efficiency particulate air (HEPA) filters, the data are conflicting. Although steam cleaning of carpets or use of acaricides can kill mites, the reduction tends to be incomplete and short-lived. Freezing stuffed animals, blankets, or clothes should be effective, but controlled trials have not been reported (8). However, washing is required to remove the allergen from these items. Vacuum cleaning does help to reduce the overall allergen burden (10).

TABLE 13.1 CONTROL MEASURES TO REDUCE HOUSE DUST MITE EXPOSURE

Encase pillows, mattress, and box springs in allergen nonpermeable cover (<10 µm pore fine woven)

Wash bed linens weekly in water <120°F or tumble dry linens at ≥130°F for 10 min

Keep indoor humidity at 35%–50%
Regular vacuuming with HEPA cleaners or vents to the outside
Inform patients that carpets are reservoirs for mites; polished floors (e.g., linoleum, hardwood, terrazzo) are therefore the flooring of choice, especially important in the bedroom
Do not recommend use of acaricides or HEPA filtration alone
Discourage bunk beds
HEPA, high-efficiency particulate air.

Mold Spores

Exposure to mold spores may also be reduced by environmental precautions (11). The patient should avoid entering barns, mowing grass, and raking leaves because high concentrations of mold spores may be found there. Indoor molds are particularly prominent in humid environments. Bathrooms, kitchens, and basements require adequate ventilation and frequent cleaning. If the patient's home has a humidifier, it should be cleaned regularly so that mold does not have an opportunity to grow. Humidity should ideally be 35% to 50%. Water-damaged furnishings or structural elements should be completely replaced to avoid mold growth. More controlled studies are needed to evaluate interventions for fungal-related health effects (11).

Cockroach Allergens

Control of cockroach allergen exposure may be very difficult, especially in the inner city. The 2013 practice parameter gives some advice about reduction of exposure to cockroaches (5). Exposure to cockroach allergen should be minimized to reduce the risk of sensitization, allergic disease, and asthma morbidity. Cockroach numbers can be monitored by using sticky traps. There should be mitigation of factors known to facilitate persistence of cockroach populations: food, water, and paths of ingress. Pesticides should be used carefully; ideally, a professional exterminator should be involved in an integrated pest management program. Reservoirs of cockroach contaminants

should be cleaned or removed.

Furry Animal Allergens

A 2012 practice parameter relative to furry animals offers several recommendations about exposure control (7). Avoidance is the best way to manage cat and dog allergy. To reduce cat allergen exposure, a combination of the following measures may be helpful: removing reservoirs, HEPA air cleaners, improved ventilation, mattress, and pillow covers. The following measures can reduce airborne cat and dog dander on surfaces, but the clinical benefit is unproven: tannic acid or hypochlorite bleach application. Because one or more allergens are present in all cats and dogs, patients should not be advised that it is safe to get a nonallergenic cat or dog.

Rodent Allergens

Rodent exposure can lead to sensitization and allergic disease. There are a limited number of avoidance strategies that are evidence-based (6). Habitat modification should be performed to remove water, food, shelter, and means of rodent ingress. Rodent traps are a way to remove rodents from infested buildings. If other interventions are not effective, rodenticides should be used as part of an integrated pest management technique. In terms of laboratory animal handlers, rodent allergen exposure should be reduced by engineering controls, staff training, and personal protective equipment.

Other Inhalant Allergens

Other airborne allergens, such as tree, grass, and ragweed pollens, cannot be avoided except by staying out of geographic areas where they pollinate. For most individuals, this is impractical socially and economically. Air-conditioning and air-filtration systems, showering, and changing clothes reduce but do not eliminate exposure to these pollens.

IMMUNOTHERAPY

Immunotherapy, a term introduced by Norman and coworkers (12), does not imply a mechanism. It consists administration of allergen to which the patient has type I immediate hypersensitivity. As a result of the allergen administration, the patient is able to tolerate exposure to the allergen with fewer symptoms. The mechanism by which this improvement occurs has not been definitely established. However, over the years, several mechanisms have been postulated to account for the improvement. Immunotherapy was first used by Noon and

Freeman, who observed that pollen was the etiologic agent of seasonal rhinitis and that immunization was effective in the treatment of various infectious diseases, including tetanus and diphtheria.

Immunotherapy was used empirically by physicians over the ensuing 40 years. Cooke (13) observed that cutaneous reactivity was not obliterated by allergy injections. Cooke (14) also discovered a serum factor, which he called "blocking antibody," in the serum of patients receiving immunotherapy. This serum factor could inhibit the passive transfer of allergic antibody described by Prausnitz and Küstner. However, there was not a constant relationship between blocking antibody titers and symptom relief.

The first controlled study of the efficacy of immunotherapy by Bruun (15) was published in 1949. Within a short time, *in vitro* techniques were developed to assess objectively the immunologic results of immunotherapy. Many immunologic changes occur as a result of immunotherapy (Table 13.2). Which changes are responsible for the efficacy of immunotherapy is unknown (16). Two general types of immunotherapy exist: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT).

SCIT and SLIT

In general, immunotherapy is indicated for clinically significant disease when the usual methods of avoidance and medication are inadequate to control the symptoms (Table 13.3). It is considered to be effective in ameliorating symptoms of allergic rhinitis, allergic conjunctivitis allergic asthma, and Hymenoptera sensitivity. These topics are discussed in Chapters 15, 19, 26, and 28, respectively. There is limited evidence that immunotherapy is an effective therapy for atopic dermatitis (16,17).

The gold standard has been SCIT; in the past three decades, SLIT has been studied and reported to be a safe and effective alternative (18). In contrast to pharmacologic therapy, SCIT and SLIT actually modify disease and have been reported to have benefits that can last for years after discontinuation of therapy. In addition to improving existing symptoms of allergic rhinitis, conjunctivitis and asthma, SCIT and SLIT have been reported to prevent new allergic sensitizations as well as development of asthma in patients with rhinitis (19–21). While there have been no large controlled head-to-head trials comparing SCIT and SLIT, most meta-analyses suggest that SCIT is more efficacious while SLIT is safer (22). In the United States, the only Food and Drug Administration (FDA)-approved SLIT therapies are single allergen tablets of grass or ragweed

(23).

There have been several Cochrane systematic reviews (SRs) comparing the efficacy and safety of SCIT and SLIT to placebo. In seasonal rhinitis treated with SCIT, 51 of 1,111 publications met criteria for inclusion (24). There was significant reduction in both symptom and medication scores. Most adverse reactions were mild. There were 19 events in the SCIT group requiring epinephrine (0.13% of 14,085 injections), and one event in the placebo group (0.01% of 8,278 injections). A Cochrane SR of SCIT for perennial rhinitis has been reported (25). While there was no effect on medication scores, there was a significant reduction in symptoms scores as well as combined symptom and medication scores in the SCIT group. Most reactions were mild. However, eight Grade 4 reactions occurred and all were in the SCIT group. A Cochrane SR evaluated SLIT as a treatment for seasonal or perennial allergic rhinitis (26). Significant reductions were found in both symptom scores and medication requirements in those treated with SLIT. Most reactions were mild, local pruritus that resolved within a week or so; there were 93 documented episodes of wheezing or worsening asthma and no reported reactions required the use of epinephrine. There is also a Cochrane SR evaluating SLIT for asthma, which concludes that lack of data for important outcomes like asthma exacerbation and quality of life have limited our ability to draw a clinically useful conclusion (27). A meta-analysis of SCIT in asthma concluded that immunotherapy was efficacious (28).

TABLE 13.2 IMMUNOLOGIC CHANGES WITH IMMUNOTHERAPY

Increased allergen-specific IgA and IgG, especially IgG4

Decreased allergen-specific IgE after prolonged therapy

Decreased seasonal rise of specific IgE

Decreased IL-4 and IL-13 from effector cells

Decreased allergen-induced basophil histamine release

Increased regulatory T cells (CD4$^+$, CD25$^+$, FoxP3$^+$) that produce IL-10, TGF-β, or both

Reduced response of skin, conjunctiva, and respiratory mucosa to allergen challenge
Change of CD4$^+$ cells from the T$_H$2 to the T$_H$1 phenotype
Reduced binding of allergen–IgE complexes by CD23$^+$ B cells which reduces antigen presentation

TABLE 13.3 INDICATIONS FOR AEROALLERGEN IMMUNOTHERAPY

IgE-mediated disease (allergic rhinitis, allergic conjunctivitis, or allergic asthma)
Significant symptomatology in terms of duration and severity
Avoidance not possible
Pharmacologic therapy unsatisfactory
Availability of high-potency extract, appropriate dosage schedule, and compliant patient

IgE, immounogloblin E.

Choice of Allergens

The aeroallergens that are commonly used in immunotherapy of allergic rhinitis or allergic asthma include extracts of house dust mites, mold spores, and pollen from trees, grasses, and weeds. The pollen species vary with geographic location, and this information concerning regional aerobiology can be obtained from Chapter 7 and on websites such as the National Allergy Bureau (http://www.aaaai.org/nab). Because the population is quite mobile, it is usual practice to perform a skin test and treat with common, important allergens outside a physician's geographic location as well as those in the local environment. For instance, there is no Bermuda grass in Chicago. However, it is a potent allergen in the southern United States, Hawaii, Mexico, and the Caribbean, where people often vacation. Thus, it is used in skin testing and

treatment of patients in Chicago. In the allergic evaluation, a patient undergoes skin testing with various allergens. Skin testing has several advantages over *in vitro* immunoassays. The skin test results are available immediately, a variety of allergen extracts can be used, and it is a relevant biologic response. Previously, it was the case that skin testing was more sensitive, but that is no longer true (29). However, because of the other advantages, skin tests are preferred for the diagnosis of IgE-mediated sensitivity (30). If the patient's history of exacerbations temporally corresponds to the skin test reactivity, the patient probably will benefit from immunotherapy. For example, a patient having a positive grass skin test, rhinorrhea, and palatal itching in May and June in the Midwest will benefit from grass pollen immunotherapy. In contrast, a patient with an isolated positive grass skin test and with perennial symptoms of rhinorrhea and nasal congestion probably has vasomotor rhinitis and will not benefit from immunotherapy.

Many patients have allergic rhinitis or allergic asthma from various types of animal dander. Avoidance is the most appropriate therapeutic maneuver for such patients. In some instances, avoidance is unacceptable; and immunotherapy with animal dander may be given. Patients who are very sensitive to dander extracts may have problems with local or systemic reactions, such that it is difficult to attain clinically efficacious doses (31).

Technical Aspects

Allergen Extract and Tablet Potency

The preparation and distribution of allergen extracts, also called *vaccines*, is regulated in the United States by the FDA, Center for Biologics Evaluation and Research (CBER). This agency has developed reference standards for a number of allergen vaccines and reference serum pools to be used by manufacturers to standardize their vaccines. The potency is initially established by an end-point titration technique called the ID_{50} EAL method. Based on these results, the extract is assigned a biologic allergy unit (BAU) potency. Subsequently, allergen extract manufacturers use *in vitro* assays to compare their extracts to the CBER references, and a BAU potency is assigned on the basis of these tests, most commonly enzyme-linked immunosorbent assay (ELISA) inhibition (32). Two dust mite extracts, the timothy SLIT tablet available in the United States and eight grass extracts are standardized in this way. The five-allergen grass tablet available in the United States is standardized by "index of reactivity" (IR) units. An allergen extract contains 100 IR units if it induces a wheal diameter of 7 mm

(geometric mean) in 30 patients sensitized to the allergen. Short ragweed and cat extracts (both hair and pelt) are standardized by major allergen content, unit per milliliter of *Amb a 1* or unit per milliliter of *Fel d 1*, respectively. Other aeroallergen preparations made in the United States are currently not required to be standardized. Several unitage systems are currently in use (Table 13.4).

Neither of the common unitages, protein nitrogen unit (PNU) or weight per volume (W/V), is necessarily an indicator of potency. Potency can be measured in a number of ways: cutaneous end-point titration, immunoassay inhibition, or content of a known major allergen like antigen E (*Amb a 1*) in ragweed, or *Fel d 1* in cat extracts (16). Standard extracts, including short ragweed and *Dermatophagoides pteronyssinus*, have been developed by the Allergen Standardization Subcommittee of the International Union of Immunologic Societies (32). These extracts have been extensively tested for allergen content and immunologic properties and have been assigned an arbitrary unitage—international units (IU). Until reference standards and exact quantitation of potency can be established for all extracts, less exact methods such as W/V will continue to be used.

SLIT Dose Schedule

There are two allergen preparations that have generally been used for SLIT. One preparation, SLIT drops, is an aqueous or glycerinated liquid that is held under the tongue for a specified amount of time; the remaining liquid is then either swallowed or expectorated. The doses of allergen used in SLIT drops trials varies over 1,000-fold, outcome measures are not uniform, and the preparations are often not standardized. Due to the variability of published studies, a single SLIT drops dosage schedule does not exist.

Another preparation, SLIT tablets, is a dissolvable tablet that is placed under the tongue until it dissolves entirely. The SLIT tablets available in the United States are standardized, as are the dosage schedules, which have been reported to be efficacious for allergic rhinitis (33). The ragweed tablet contains 12 µg *Amb a 1* and is approved for ages 18 to 65. The timothy grass tablet (ages 5 to 65) contains 2,800 BAU, and the five-allergen grass tablet (ages 10 to 65) contains 100 or 300 IR units. The 100 IR tablet is for dose escalation in children aged 10 to 17. The dosage schedules are available in the product package inserts; there is no build-up phase except for children aged 10 to 17 using the five-allergen grass tablet. In general, tablets are taken once a day starting 3 to 4 months prior to the pollen season and continued through the pollen season. The first dose is administered under medical observation for at least 30 minutes. Subsequent

doses are taken daily, preferably at the same time of day.

TABLE 13.4 ALLERGY EXTRACT UNITAGE

UNITAGE	DERIVATION OF UNIT
Weight-to-volume ratio (W/V)	Weight (in g) extracted per volume (in mL)
Protein nitrogen unit (PNU)	0.01 μg of protein nitrogen
Biologic allergy unit (BAU)	Based on average skin test end point of allergic individuals
Major allergen unit	Based on the amount of a major allergen in the extract
Biologic unit (BU)	Based on skin tests end point relative to histamine
International unit (IU)	Based on *in vitro* assays relative to World Health Organization standard allergenic preparations

Patients should be informed about possible adverse effects: local mucosal effects including oral pruritus, mouth edema, tongue swelling, oropharyngeal edema, and even anaphylaxis. Eosinophilic esophagitis has also been reported (34). It is recommended that patient be prescribed an epinephrine auto-injector. If patients develop oral inflammation (e.g., mouth ulcers, dental surgery), it is recommended that the patient stop SLIT until the inflammation is completely healed. Tablets are contraindicated in patients whose asthma is severe, uncontrolled, or unstable. The optimal duration of SLIT tablet therapy has not yet been defined.

SCIT Dose Schedule

Allergen extracts may be given individually or may be mixed in one vial. That is, a patient receiving immunotherapy to grass pollen and tree pollen could receive two injections, one of grass and one of tree, or could receive one injection containing both grass and tree pollens. The latter is almost always preferable for patient comfort. Because mold extracts contain proteases that may influence

other extracts like pollens and dust mite, some recommend giving mold as a separate injection (16). Most clinicians in the United States administer allergen immunotherapy subcutaneously, beginning with weekly or twice-weekly injections (16). Current evidence suggests that treatment with higher doses of pollen extracts results in better long-term reduction of clinical symptoms and greater immunologic changes than low-dose therapy. In general, 15 to 25 µg of major allergen protein are required for clinically significant improvement in symptom and medication scores (35). There are no clear data on the optimal length of time immunotherapy should be continued. Most patients who are maintained on immunotherapy and show improvement through three annual pollen seasons continue to maintain improvement even when their injections are discontinued (16). Patients who do not respond after receiving maintenance doses of immunotherapy for 1 year are unlikely to improve with further treatment. Therefore, immunotherapy should be discontinued in patients who have not had appreciable improvement after an entire year of maintenance doses.

The most common method of administering perennial immunotherapy is subcutaneously using a dose schedule similar to that in Table 13.5. Very sensitive patients must begin at 1:100,000 W/V. The injections are given weekly until the patient reaches the maintenance dose of 0.50 mL of 1:100 W/V. At that point, the interval between injections may be gradually increased to 2 weeks, 3 weeks, and ultimately monthly. When a new vial of extract is given to a patient receiving a maintenance dose of 0.50 mL of 1:100 W/V, the volume should be reduced to about 0.35 mL and increased by 0.05 mL—each injection to 0.50 mL. The reason for this is that the new vial may be more potent. There are patients whose achievable maintenance dose is lower than the standard shown in Table 13.5.

Accelerated dosage schedules have also been published; they generally require preteatment (16). In *rush immunotherapy* schedules, the starting doses are similar to those in Table 13.5, but patients receive injections at intervals varying between 15 and 60 minutes over 1 to 3 days until the target therapeutic dose is reached. In *cluster immunotherapy* schedules, the initial dosages are similar to those in Table 13.5, and the visit frequency is usually once or twice weekly; however, at each visit, more than one injection is administered, with the interval between injections varying from 30 minutes to 2 hours. The advantage of both rush and cluster regimens is that the maintenance dose can be achieved more quickly; the cluster regimen can be especially useful in treating a patient who resides at a significant distance from the physician's office. The disadvantage of both cluster and rush regimens is that the reaction rate is

somewhat higher than with more conventional schedules (16). For patients on those regimens, initial doses from new vials should also be reduced. Allergen extracts should be kept refrigerated at 4°C for retention of maximum potency. If a vial freezes or heats above 4°C, it should be discarded because the allergens may be altered.

Procedures for Injections

Immunotherapy injections should be given only after the patient, the patient's dose schedule, and the patient's vial have been carefully identified because improper dose is a common cause of allergic reactions to immunotherapy. Injections should be given with a 1-mL syringe so that the appropriate dose can be given accurately. The injection should be subcutaneous with a 26-gauge needle. Before injecting material, the plunger of the syringe should be withdrawn; if blood appears, the needle and syringe should be withdrawn and discarded. Another needle and syringe should be used for the injection. Patients should be observed at least 30 minutes after their injections for evidence of reactions.

TABLE 13.5 **EXAMPLE OF AN SCIT DOSAGE SCHEDULE**

DATE	EXTRACT CONCENTRATION (W/V) (APPROX.)	EXTRACT CONCENTRATION (BAU/mL)	MAJOR ALLERGEN CONCENTRATION (µG/mL)	VOLUME	REMARKS
	1:100,000	1	0.04	0.1	
				0.2	
				0.4	
				0.8	
	1:10,000	10	0.4	0.05	
				0.10	
				0.15	

			0.20
			0.30
			0.40
			0.50
1:1,000	100	4.0	0.05
			0.10
			0.20
			0.30
			0.40
			0.50
1:100	1,000	40	0.05
			0.10
			0.15
			0.20
			0.25
			0.30

	0.35
	0.40
	0.45
	0.50

BAU, biologic allergy unit; W/V, weight-to-volume ratio.

Reactions

Small local reactions with erythema and induration less than 20 mm are common and are of no consequence. Large local reactions and generalized reactions (e.g., rhinitis, conjunctivitis, urticaria, angioedema, bronchospasm, and hypotension) are cause for concern. Large local reactions generally can be treated with H1 antihistamines and local application of ice. Rarely, significant swelling occurs such that 2 days of oral steroids are prescribed. Generalized reactions consisting of bronchospasm, angioedema, or urticaria usually respond to 0.3 mL of 1:1,000 epinephrine subcutaneously, but intramuscular epinephrine into the vastus lateralis is recommended if the patient doesn't recover quickly. The dose for children weighing up to 30 kg is 0.01 mL/kg. This may be repeated every 5 or 15 minutes for up to three doses.

Practice parameters for the diagnosis and management of anaphylaxis have been published (36). If the patient has laryngeal edema and is unresponsive to epinephrine, intubation or tracheostomy is necessary. If the patient has hypotension unresponsive to epinephrine, the administration of intravenous fluids and pressors is necessary. Physician who administers allergen injections must be prepared to treat serious anaphylactic reactions should they occur. If a patient has a large local reaction, the subsequent dose should be reduced or repeated, based on clinical judgment. If a systemic reaction occurs, the dose should be reduced to one-half to one-tenth the dose at which the reaction occurred before proceeding with subsequent slow increase. The management of local and systemic reactions is outlined in Table 13.6. Because of local or systemic reactions, there are patients who are unable to tolerate usual maintenance doses and must be maintained on a smaller dose, for instance, 0.20 mL of 1:100 W/V.

The safety of immunotherapy has been questioned. In one report, five of nine patients who developed polyarteritis nodosa had received immunotherapy (37). Asthma, however, may be the first symptom of polyarteritis nodosa, and the latter disease may have been present subclinically before the start of the injection therapy. If the polyarteritis nodosa were directly related to immunotherapy, an immunologic mechanism must be postulated, the likely one being antigen–antibody complex damage. However, the amount of antigen used in standard immunotherapy is far less than that producing antigen–antibody complex damage in experimental animals.

Another study compared a group of atopic patients receiving immunotherapy for at least 5 years with a group of atopic patients not on injection therapy (38). The treated group did not show an increased incidence of autoimmune, collagen vascular, or lymphoproliferative disease. There were no adverse effects on immunologic reactivity as measured by several laboratory immunologic tests. Appropriate immunotherapy is accepted as a safe therapy.

Special Considerations

Pregnancy

Patients doing well on maintenance doses of immunotherapy who become pregnant can be continued on immunotherapy (39). However, if a pregnant patient is not on immunotherapy, the risks and benefits need to be evaluated and the decision when to initiate immunotherapy individualized.

TABLE 13.6 MANAGEMENT OF REACTIONS TO IMMUNOTHERAPY

Local reactions

1. Oral antihistamine

2. Local application of cold

3. Review of dosage schedule

Systemic reactions (including generalized erythema, urticaria, angioedema, bronchospasm, laryngeal edema, shock, and cardiac arrest)

1. 0.01 mL/kg up to 0.2 mL aqueous adrenalin, 1:1,000 subcutaneously, at site of immunotherapy injection to slow absorption of antigen

2. 0.01 mL/kg up to 0.3 mL aqueous adrenalin, 1:1,000 IM or subcutaneously, at another site

3. Diphenhydramine intravenously or intramuscularly, 1.25 mg/kg–50 mg

4. Tourniquet above the site of injection of allergen

5. Specific reaction

    a. Bronchospasm: inhaled albuterol solution 0.5%, aqueous hydrocortisone 5 mg/kg up to 200 mg intravenously; oxygen

    b. Laryngeal edema: oxygen, intubation, tracheostomy

    c. Hypotension: vasopressors, fluids (0.9% normal saline), corticosteroids

    d. Cardiac arrest: resuscitation, sodium bicarbonate, defibrillation, antiarrhythmia medications

6. Review of dosage schedule

Medications

Because patients who receive immunotherapy may require treatment with epinephrine, the risks and benefits of concomitant drug therapy must be considered. For example, the *Physician's Desk Reference* cautions that monoamine oxidase inhibitors should not be administered in conjunction with sympathomimetics (40). Also, β-blocking agents and possibly angiotensin-converting enzyme inhibitors could make the treatment of anaphylaxis more difficult in some cases (36,41). Prospective and retrospective studies of SCIT for allergens haven't demonstrated increased risks of systemic reactions (36). For some patients, continuation of these medications would be acceptable because the risk–benefit ratio favors treatment, such as for venom immunotherapy (36).

Failure

If a patient has been on maintenance doses of immunotherapy for 12 months and has no improvement, the clinical allergy problem should be reassessed. Perhaps a new allergen such as an animal has been introduced into the environment. Possibly the patient has developed new sensitivities for which he or she is not receiving immunotherapy or perhaps the patient's disease is not allergic in origin but is nonallergic rhinitis or nonallergic asthma, neither of which is altered by immunotherapy. It is possible the patient may have misunderstood the benefits of immunotherapy. That is, symptom reduction, not symptom eradication, is all that can be expected from immunotherapy. It is important that the patient understand this at the initiation of therapy.

Alternate Administration Routes

In addition to the administration of allergen through the subcutaneous and sublingual routes, several other routes have been evaluated. Nasal, bronchial, intraepithelial, oral, rectal, transcutaneous, and intralymphatic immunotherapy have all been reported (42–44).

Modified Allergens

Except for in the United States, most immunotherapy in industrialized nations is given as some type of modified allergen. Although immunotherapy with aqueous antigens has demonstrated efficacy, it is still a long, expensive process with a risk for severe systemic reactions. Therefore, polymerized allergens, formaldehyde-treated allergens, allergens conjugated to alginate, and other forms of modified immunotherapy are used, except in the United States, where such allergens could not be characterized to the satisfaction of FDA/CBER.

Administration of purified antigens, for instance, antigen E of short ragweed, was tried as a possible improvement of immunotherapy. Improvements similar to those obtained with whole extracts but with fewer reactions and injections were found with antigen E. The expense of the antigen E purification process has made this sort of administration impractical. Recombinant allergens have also been produced (45). Recombinant allergens have been reported to be effective (43,46).

There are basically four avenues of research to improve immunotherapy. The first is the development of hypoallergens that induce IgG4 and T-cell tolerance but do not cross-link IgE on the surface of mast cells (46). Glutaraldehyde polymerized allergens are hypoallergens (47). Patterson and colleagues

polymerized ragweed and other pollen proteins with glutaraldehyde. Because there are fewer molecules of polymer on a weight basis compared with monomer allergens, there are fewer molecules to react with histamine-containing cells. There are data that demonstrate an efficacy of polymer equivalent to that of monomer with fewer injections and fewer systemic reactions (47). There are also data demonstrating efficacy of polymerized ragweed in double-blind histamine placebo-controlled trials. This therapy is available in countries other than the United States. Through genetic engineering, hypoallergens have been created, retaining T-cell reactivity with reduced IgE binding.

Another avenue is to use T-cell peptides to induce tolerance (48). A third approach is to identify B-cell peptides that are not IgE-dominant epitopes and fuse them to immunogenic carrier proteins. The resulting vaccines induce IgG4 without activation of allergen specific T cells (49). A final approach is the use of adjuvants to modulate the Th2 response to another T-cell helper type, usually Th1 or Treg. Among the adjuvants that have been studied are aluminum hydroxide, oil emulsions, lipid-based vesicles such as liposomes, particulate delivery systems such as nanoparticles, vitamin D, and Toll-like receptor agonists including unmethylated CpG and monophosphoryl Lipid A (46).

Novel Therapies

Novel therapies, such as anti-IgE, anti–interleukin-5 (anti–IL-5), sIL-4, other human recombinant engineered proteins, immunostimulatory sequences of DNA, and peptide immunotherapy are discussed in Chapter 38.

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Anaphylaxis and Other Generalized Hypersensitivity

CHAPTER **14**

Anaphylaxis
KRIS G. MCGRATH

■ ## HISTORY AND DEFINITION

Anaphylaxis is the most severe allergic presentation and a true medical emergency. This adverse event occurs rapidly, often dramatically, and is seldom anticipated. Death, though rare, may occur with mild symptoms progressing rapidly to cardiovascular and respiratory arrest. The definition of anaphylaxis has evolved since the discovery of immunoglobulin E (IgE); similar clinical presentations may have different immunopathogenic mechanisms. Anaphylaxis is defined as a serious, life-threatening, generalized or systemic, hypersensitivity reaction that is rapid in onset and may cause death. Traditionally, anaphylaxis is caused by IgE-mediated immunologic release of mediators from mast cells and basophils. Anaphylactoid, on the other hand, is a clinically similar event not mediated by IgE. In 2003, the World Allergy Organization dropped the term "anaphylactoid," calling all anaphylactic episodes as immunologic and nonimmunologic. Simons in 2006 suggested a separate category "idiopathic," which is neither immunologic nor nonimmunologic. All terms and definitions remain in use; consortium of experts assembled from multiple specialties defined anaphylaxis as "a condition caused by an IgE-mediated reaction," and noted that such reactions "are often life-threatening and almost always unanticipated." The

task force included the following clause in the definition: "an injection of epinephrine is indicated for the management of a patient exhibiting signs and symptoms of an anaphylactic event" (1–7).

In 1902, Paul Portier and Charles Richet observed that injecting a previously tolerated sea anemone antigen into a dog produced a fatal reaction as opposed to the anticipated prophylaxis. They termed this phenomenon "anaphylaxis," the antonym of prophylaxis (Greek *ana*, meaning "backward," and *phylaxis*, meaning "protection"). They observed two factors likely essential for anaphylaxis: increased sensitivity to a toxin after previous injection of the same toxin and an incubation period of at least 2 to 3 weeks. Charles Richet was recognized as the founder of the new science of allergy and was awarded the Nobel Prize in 1913 and also honored on a French stamp issued in 1987 (8–10).

Anaphylaxis is a modern disease with sparse case reports during 17th to 19th centuries. In the 20th century, anaphylaxis predominately occurred in health-care settings from injections of biologic medications, such as tetanus and diphtheria antitoxins. In the 1950s and 1960s, anaphylaxis occurred from medications, diagnostic agents, insect venoms, and food (7,11–13). Reports of idiopathic anaphylaxis (IA) were published in the 1970s, followed by reports of anaphylaxis triggered by exercise, exercise in combination with food, and natural rubber latex in the 1980s. Contemporary reports of anaphylaxis continue to increase, primarily resulting from food allergy in children, use of biologic medicines such as humanized monoclonal antibodies, and administration of anticancer chemotherapy drugs, and less from natural rubber latex (7,11,13–18). Development of modern drugs, biologic medications, and diagnostic agents, and the use of herbal and natural remedies have resulted in increased incidences of anaphylaxis. Application of these agents by health-care providers, pharmacists, and general public requires acute awareness of anaphylaxis and also knowledge of preventative and therapeutic measures.

All forms of anaphylaxis present the same symptoms, requiring similar rigorous diagnostic and therapeutic interventions (19). Refer to Table 14.1 for types and examples of anaphylaxis.

There are limited studies discussing the role of genetic factors in anaphylaxis: e.g., KIT mutations restricted to bone-marrow mast cells in patients with indolent systemic mastocytosis without skin manifestations, and anaphylaxis triggered exclusively by insect stings (20–24). The following factors and amplifying cofactors are associated with increased risk of anaphylaxis and anaphylaxis fatality:

TABLE 14.1 SOME CAUSES OF ANAPHYLAXIS IN HUMANS

Immune-IgE, FcεR1 Mediated

Foods: peanut, tree nuts, shellfish, fish, egg, sesame, food additives—spices, vegetable gums, colorants (carmine), papain, food-dependent exercise, etc.

Antibiotics: β-lactam antibiotics, sulfonamides, neuromuscular blocking agents, etc.

Chemotherapy: taxanes, epipodophyllotoxins, asparginase, doxorubicin, etc.

Monoclonal antibodies: omalizumab, rituximab, infliximab, trastuzumab, etc.

Formulation vehicle: Cremophor EL

Immunotherapy extracts: pollens, dust mite, mold, animal, venom

Biologics: vaccines (or excipient-egg, gelatin), enzymes, hormones, horse antilymphocyte globulin, seminal fluid

Insect sting/bite, other bites: Hymenoptera, fire ant, jellyfish, scorpion, snake, other

Natural rubber latex: gloves, condoms

Inhalants: grass pollen; peanut; horse, cat, and hamster dander (rare)

Immune-non-IgE, FcεR1 Mediated-Multimediator Recruitment: Clotting, Complement, Clot Lysis, Kallikrein-Kinin Contact System

Heparin contaminants: oversulfated chondroitin sulfate–kallikrein–kinin contact system

Dialysis exposure: AN69 membrane–kallikrein–kinin contact system

Colloid plasma expanders: dextran, hydroxyethyl starch–direct mast-cell release, complement-mediated, immune aggregate

Blood products: IgG anti-IgA antibody, immune complex, cytotoxic

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs): disturbance of arachidonic acid metabolism

Nonimmune: Direct Release of Mediators from Mast Cells and Basophils

Drugs: opiates

Diagnostic agents: radiocontrast media (also possible IgE-FcεR1, activation of kallikrein–kinin contact system), sulfobromophthalein

- The nature of the antigen: Certain antigens more often cause anaphylaxis, such as drugs, e.g., β-lactam antibiotics, neuromuscular blocking agents (NMBAs), and foods, e.g., peanuts, tree nuts, finned fish, shellfish, sesame, egg, and milk.

- Parenteral administration of a drug more likely results in anaphylaxis compared to oral ingestion.

- Atopy and asthma: Fatal anaphylaxis because of foods is associated with asthmatic exacerbations in patients taking daily treatment for asthma; in some cases, treatment is suboptimal.

- An atopic history is a risk factor for anaphylaxis (and greater risk of recurrence) from latex, food, exercise, idiopathic, radiographic contrast media (RCM), and hymenoptera.

- Repeated intermittent courses of treatment with a specific substance can be a risk factor. The longer is the duration since the last antigen exposure, the lesser is the risk.

- Immunotherapy (IT) extract injection to an asthmatic, especially symptomatic or with a forced expiratory volume in 1 second ≤70% predicted.

- Gender: Males at the age of <15 are at greater risk of anaphylaxis, whereas females at the age of >15 are at greater risk. Females have a higher risk for anaphylaxis resulting from latex, NMBAs, RCM, as well as idiopathic and overall anaphylaxis. The male to female ratio for insect anaphylaxis is 60:40. The male sex is a risk factor for death by hymenoptera-induced anaphylaxis.

- Anaphylaxis is more common in community than health-care settings.

- Age and anaphylaxis fatality: Infants, teenagers, pregnant women, and elderly are at higher risk for anaphylaxis. Fatalities from food-induced anaphylaxis are higher in adolescents and young adults. Being an adolescent and having

uncontrolled asthma with cofactors of noncompliance with asthma reliever medication, exercise, fasting, denial of symptoms, and delay in seeking help. Fatalities are more predominate in middle-aged and older adults from anaphylaxis triggered by insect stings, diagnostic agents, and medications; a cofactor may include monotherapy with β-blockers and to a lesser extent, angiotensin converting enzyme inhibitors (ACEi), with risk further increased if taking a β-blocker and an ACEi concurrently.

• Stinging insect anaphylaxis risk is increased by stinging insect species, recent stings, comorbidity of asthma, chronic obstructive pulmonary disease, mastocytosis, mast-cell activation syndrome, and concurrent use of a β-blocker.

• A history of prior anaphylaxis.

• Cofactors that potentially amplify anaphylaxis are exercise, use of ethanol, nonsteroidal anti-inflammatory drugs (NSAIDS), acute infections, stress, perimenstrual status, exposure to extremes of temperature or humidity, high pollen counts, foreign travel or other disruption of routine, feeling unwell, fever, or acute infection.

Comorbidities that increase the risk of anaphylactic fatality include asthma, cardiovascular disease, mastocytosis, thyroid disease, acute infection, decreased host defenses, reduced level of platelet-activating factor (PAF) acetylhydrolase activity, and activating KIT mutations (7,11,20,25). Mental health and emotional stress may impair recognition of the clinical presentation. Multiple concurrent factors may play a role, e.g., an elderly patient with cardiovascular disease taking a new medication or combination of medications, such as a β-blocker with an ACEi. Concurrent trigger plus a cofactor may also be present, e.g., a specific food in combination with exercise (20,26).

EPIDEMIOLOGY

Studies of incidence and prevalence of anaphylaxis have included database mining, population-based questionnaires, chart and systemic reviews, and meta-analyses. Despite robust data collection, limitations exist in the estimation of incidence and prevalence of anaphylaxis owing to the multiple diagnostic criteria for anaphylaxis and heterogeneity of the study populations. Additionally, the use of diagnostic codes, currently limited to ICD9 and ICD10 codes, has misclassified anaphylaxis and can lead to under- or over-reporting. The 11th revision, *ICD-11*, will likely improve the classification and coding of hypersensitivity and allergic diseases adding validity to future epidemiologic

studies (22,27,28).

The estimated lifetime risk of anaphylaxis is at least 1.6%, and the incidence of anaphylaxis ranges from 6.7 to 112.2 episodes per 100,000 person-years from a review based on population-based findings obtained from regional databases, health maintenance organizations, and large primary-care databases (29). In Yu and Lin's review of the epidemiology of anaphylaxis, the frequency of anaphylaxis presenting to the emergency department has risen over the past several years by 58%, and anaphylaxis episodes occurred mostly at home, and unfortunately many patients may never present to a physician, suggesting that the exact incidence of anaphylaxis in the community may likely be underestimated (22). According to data from the U.S. Healthcare Cost and Utilization Project Kids' In-Patient Database, the frequency of hospital admissions for food-induced anaphylaxis in children (<18 years) more than doubled from 2000 to 2009 (14). Nonfatal all-cause anaphylaxis hospital admissions in England and Wales increased by 615% from 1992 to 2012 (30,31). Similar to the trends in the United States, the UK, and history in Australia, Mullins and colleagues confirmed a 1.7-fold increase in overall food-related anaphylaxis admissions in Australia, increasing over time an additional $0.36/10^5$ person-year in 1998 to 1999 (all ages) to 0.48 (2004 to 2005) and 0.62 (2011 to 2012). Age-specific changes were significant in those aged 5 to 14 and 15 to 29 years (32).

An analysis of the U.S. Death Database from 1999 to 2010 suggested that fatal anaphylaxis during this time period was mostly due to the use of medications, followed by unspecified anaphylaxis, venom-induced anaphylaxis, and food-induced anaphylaxis. The overall prevalence of fatal anaphylaxis was 0.69 persons per million (33). The probability of dying from anaphylaxis is very low (0.3 to 2%), however, a significant number of deaths have been reported in older age groups, often preceded by nonfatal episodes implying possible prevention (29).

Foods are the most common anaphylaxis trigger in infants, children, teens, and people in their 20s. From a meta-analysis of data from 34 studies, the incidence rate of food-induced anaphylaxis has been found to be 0.14 per 100 person-years at all ages, and up to 7 per 100 person-years in children aged 0 to 4 years (30,31). Outpatient fatal anaphylaxis is more commonly associated with food, whereas drug-induced fatal anaphylaxis is more common in hospitalized patients (32,33). Food implicated in anaphylaxis study vary with the geographical area of the study and the age of the patients (34,35). In children,

cow's milk and hen eggs are the most common trigger food in all series. Other common food triggers of anaphylaxis vary depending on the consumption habits. For example, sesame, fish, and peanuts are common causes of anaphylaxis in children in countries where these foods are more commonly included in diet (34,36,37). In adults, the most common foods associated with anaphylaxis are peanuts, nuts, fruits, and shellfish (38–41). In the United States, the top eight food triggers of anaphylaxis are peanuts, cow's milk, shellfish, tree nuts, eggs, fish, wheat, and soy (42,43).

Food and drugs are reported to be the most frequent cause of anaphylaxis in outpatients. Drug-induced anaphylaxis is most commonly caused by NSAIDs and antibiotics, usually β-lactams (44–46).

Anaphylaxis is rare among hospitalized patients. In this setting, patients receive many drugs to treat acute illnesses, and in a study conducted by Tejedor Alonso and colleagues between 1999 and 2005, the average number of drugs causing trigger was found to be 10 to 11. In this study, female gender, young age, and admission to the vascular surgery unit favored the occurrence of anaphylaxis among hospitalized patients. Episodes of anaphylaxis tended to occur in the first 5 or 6 days. The observed crude cumulative incidence was 1.5 episodes of anaphylaxis (95% CI, 0.9 to 1.9) per 5,000 admissions (47).

An international multicenter study of 481,752 patients estimated that in-hospital anaphylaxis occurs in one out of every 5,100 admissions (48). The Boston Collaborative Drug Surveillance Program reported 0.87 anaphylactic fatalities per 10,000 patients in 1973 (49). Other hospital studies estimate anaphylaxis to occur in one out of every 3,000 patients and to be responsible for more than 500 deaths every year. Weiler estimated that out of 300 individuals expected to have anaphylaxis each year in a community of 1 million, three are expected to die (50).

In Tejedor Alonso and colleague's series, drugs were the most frequent and almost the only cause of anaphylaxis (85%) in admitted patients with metamizole and iodinated contrast media as the most commonly involved drugs in almost all age groups, and in the group overall. In this series, the drugs responsible for the absolute number of episodes of anaphylaxis did not always carry the highest risk of causing anaphylaxis (47). In an older series by Porter and Jick, the most common causes of anaphylaxis were hematologic products, asparaginase, and several other drugs, use of which has now decreased (51). In the International Collaborative Study of Severe Anaphylaxis, the most frequent causes of anaphylaxis were found to be metamizole, diclofenac, parenteral and

oral cephalosporins, amoxicillin/ampicillin, hematologic products, and ionic and nonionic iodinated RCM (48).

Not all persons who have had anaphylaxis have it again on reexposure to the same substance. Those who do may react less severely than at the initial event. Factors suggested to explain this include the interval between exposures, the route of exposure, and the amount of the substance received. The percentage of persons at risk for recurrent anaphylactic reactions has been estimated to be 10% to 20% for penicillin, 16% to 44% for RCM, and 40% to 60% for insect stings (48,52,53).

CLINICAL MANIFESTATIONS OF ANAPHYLAXIS

The onset and course of anaphylaxis may vary greatly among the victims. Symptoms and signs typically occur within 5 to 60 minutes of the inciting event. Up to 40 possible signs and symptoms may occur and differ among individuals; in the same individual, one episode may differ from the other. Death may occur suddenly from a severe episode, despite correct treatment, through upper-airway edema and asphyxiation, intractable bronchospasm, or irreversible vascular collapse (7,11,54,55). In Pumphrey's large study of anaphylactic deaths, the medium time for respiratory or cardiac arrest was 30 minutes for foods, 15 minutes for venom, and 5 minutes for iatrogenic triggers (56).

The skin, respiratory tract, cardiovascular system, and gastrointestinal tract may be affected solely or in combination. The absence of cutaneous symptoms suggests the event is not anaphylaxis, yet does exclude anaphylaxis. In addition to taking the patient's history, engage more eyes and ears by interviewing witnesses at the time of the event. In order of frequency, the clinical manifestations of anaphylaxis are as follows: cutaneous: urticarial and angioedema 62% to 90%, flushing 45% to 55%, pruritus without rash 2% to 5%; respiratory: dyspnea, wheeze 45% to 50%, rhinitis 30% to 35%, upper-airway angioedema 15% to 20%; cardiovascular: hypotension, dizziness, syncope, diaphoresis 30% to 35%; gastrointestinal: nausea, vomiting, diarrhea, abdominal pain 25% to 30%; miscellaneous: headache 5% to 8%, substernal pain 4% to 5%, seizure 1% to 2%. A myriad of other signs and symptoms occur within each of these categories, including, yet not limited to, morbilliform rash, pilar erection, dysphonia, coughing, cyanosis, dysphagia, aura of impending doom, uneasiness, behavior change, headache, tunnel vision, confusion, metallic taste in mouth, uterine cramping, and/or bleeding. Unusual presenting clinical manifestations of anaphylaxis include somnolence and chest pain in children, chest pain in adults,

and syncope and seizure without any other signs or symptoms (3, 54, 55,57—67).

Rapid cardiovascular collapse and shock can occur without cutaneous manifestations (68–70).

The National Institute of Allergy and Infectious Diseases (NIAID)/Anaphylaxis Network Definition of Anaphylaxis concluded that there were three presentations consistent with anaphylaxis: (1) an acute onset of a reaction that included the skin (mucosal tissue) and involvement of the respiratory tract and/or a decrease in blood pressure; (2) the rapid onset of a reaction after exposure to a likely allergen that involved two organ systems (respiratory tract, skin, decrease in blood pressure, and/or persistent gastrointestinal symptoms); and (3) a decrease in blood pressure alone after exposure to a known allergen. It is important to note that they also stated that "there without a doubt will be patients who present with symptoms not yet fulfilling the criteria for anaphylaxis yet in whom it would be appropriate to initiate therapy with epinephrine" (2).

Atypical anaphylaxis can present with prominent cardiac symptoms, such as chest pain in children and adults associated with electrocardiographic changes and myocardial damage (71–74). Additionally, anaphylaxis may present with abdominal manifestations as a misdiagnosis of abdominal trauma (75,76).

The initial manifestation of anaphylaxis can be loss of consciousness; death may follow in minutes (1). Sudden fatality has also been attributed to postural change during anaphylaxis, such as sitting or standing as opposed to remaining recumbent with elevated lower extremities (45). Late deaths may occur days to weeks after anaphylaxis, and are often manifestations of reperfusion injury experienced early in the course of anaphylaxis (3,7,11).

At the initiation of symptoms, it cannot be predicted whether an episode will rapidly progress, prompting early consideration of initiating epinephrine treatment even with mild symptoms or a single-system involvement (77).

In general, the later the onset of anaphylaxis, the less severe the reaction (3,78). In some patients, anaphylaxis resolves spontaneously or with treatment, only to be followed by another episode of anaphylaxis, termed "biphasic anaphylaxis." Protracted anaphylaxis may occur with persistence of symptoms for up to 48 hours despite therapy (79,80).

By using the NIAID/Food Allergy and Anaphylaxis Network (FAAN) diagnostic criteria and data from contemporary studies Lee et al. concluded that

biphasic anaphylaxis incidence is 0.4% to 2.2% in adults and 14.7% in children; median time to the biphasic event is 18.5 hours in children and 15 hours in adults; the rate of severe biphasic anaphylaxis appears to be quite low with no fatalities using the NAID/FAAN definition, however, up to 50% of patients experiencing a biphasic reaction required epinephrine administration and 8% to 14% required intensive care unit admission (2,81). An observational study reported that a subgroup of patients who had a delay in their initial epinephrine administration were more likely to develop biphasic reactions (82).

Studies vary on whether therapeutic intervention of the initial event affects the incidence of the second. There is no compelling evidence of a protective effect of corticosteroids and/or antihistamines preventing biphasic reactions. In one study, corticosteroids did not decrease emergency department return visits within 7 days and to date there is no randomized control trial that answers the question of whether corticosteroids definitively prevent a subsequent biphasic event (81,83).

Persistent, also referred to as protracted or recurrent, anaphylaxis lasts 5 to 48 hours despite therapy. The estimated rate of persistent anaphylaxis is 23% to 28%, although other investigators suggest it is less common. Protracted anaphylaxis and biphasic anaphylaxis cannot be predicted from the severity of the initial event necessitating an appropriate duration of observation and communication with the patient (84). Spontaneous recovery frequently occurs likely from endogenous compensatory mechanisms, particularly increased secretion of angiotensin II and epinephrine (7,85).

Concurrent chemical or medication use may affect recognition of anaphylaxis including ethanol, recreational drugs, sedatives, and narcotics. Mental health diseases, central nervous system diseases, and vision or hearing impairment may also impede the recognition of clinical manifestations of anaphylaxis (20).

PATHOLOGIC FINDINGS AND PATHOPHYSIOLOGY

Anaphylaxis postmortem anatomic and microscopic findings must be examined in relation to the underlying illness for which the patient was being treated, the drugs administered, and the effect of secondary changes related to hypoxia, hypovolemia, and postanaphylaxis therapy (7,11). Anaphylactic death is usually caused by respiratory arrest with or without cardiovascular collapse (48). The prominent pathologic features of fatal anaphylaxis in humans are acute pulmonary hyperinflation, laryngeal edema, upper-airway submucosal

transudate, pulmonary edema and intra alveolar hemorrhage, visceral congestion, urticaria, and angioedema. In some patients, no specific pathologic findings are found, especially if death is from rapid cardiovascular collapse. Findings observed at autopsy in Pumphrey et al. studies showed pharyngeal edema 49%, laryngeal edema 8%, and upper-airway edema 77% of cases from food anaphylaxis, 40% of venom anaphylaxis, and 30% of drug anaphylaxis. They also observed pulmonary congestion and edema in 73% of cases, whereas lung hyperinflation and mucous plugging of bronchial airways suggested that respiratory failure occurred from an asthmatic event in 26% of cases. Petechial hemorrhage (periorbital, periconjunctival, and cardiac wall) was present in 17% of cases, and brain edema was present in 26% of cases suggesting an asphyxia component of death (86,87).

Microscopic examinations reveal noninflammatory fluid in the lamina propria of the areas just described, increased airway secretions, and eosinophilic infiltrates in bronchial walls, the laminae propria of the gastrointestinal tract, and sinusoids of the spleen. Eosinophilia is often present in lung, heart, and parenchymal tissues after anaphylactic shock (86–88). Perskvist et al. (89) observed three groups of mast cells present in lung of anaphylactic death subjects: (1) those containing tryptase and chymase granules, (2) those containing tryptase granules, and (3) those containing chymase granules, noting only two groups of mast cells in subjects dying from asthma: mast cells containing tryptase and chymase and mast cells containing tryptase granules. Cutaneous erythema or angioedema is present in 5% of anaphylactic deaths. Angioedema, as well as loss of intravascular fluids, is typical from peripheral vasodilation suggesting shock has occurred, along with observations of hypoperfusion lesions of the spleen, kidneys, or other mesenteric regions (20,87,90–92). It has been reported that within 10 minutes an amount of 50% of intravascular fluid may be shifted to the extravascular space when anaphylactic shock occurs (93).

Sudden vascular collapse usually is attributed to vessel dilation or cardiac arrhythmia, but myocardial infarction may be sufficient to explain the clinical findings. Myocardial damage may occur in up to 80% of fatal cases. There are abundant mast cells present in the human heart and the mediators of anaphylaxis can produce coronary artery vasospasm; infarction can occur as a consequence of an anaphylactic episode (94,95). Kounis syndrome, initially termed "allergic angina," is the occurrence of acute coronary syndrome with allergic reactions. This syndrome may progress to acute myocardial infarction primarily in patients with underlying cardiomyopathy, however, occasionally in patients without

coronary lesions. This phenomenon has been described to occur in up to 20% of anaphylactic reactions, and has been reported to also occur secondary to biphasic anaphylaxis (96,97).

During prolonged anaphylaxis, activation of the contact system can occur with the formation of kinins with activation of the coagulation pathway and complement cascade which may prompt either blood clotting, lysis, or disseminated intravascular coagulation (DIC) as contributing causes of death (25,98).

Anaphylaxis is initiated when a host interacts with an antigen or other factors that activate mast cells or basophils, initiating degranulation and immediate (5 to 30 minutes) release of preformed mediators (histamine, tryptase, carboxypeptidase A, and proteoglycans), synthesis of arachidonic acid metabolites (prostaglandins, leukotrienes), and PAF, and delayed-phase (2 to 6 hours) generation of cytokines (TNF-α) and chemokines resulting from increased gene expression (99). The antigen or other factor can be almost anything as long as it is able to trigger the release of mediators from tissue mast cells and circulating basophils. Antigen exposure can be topical, inhaled, ingested, or parenteral. Immunologic anaphylaxis includes IgE fixing to FcεRI receptors on surface membranes of tissue mast cells and blood basophils. Receptor-bound IgE molecules aggregate and cross-link upon allergen reexposure resulting in cell activation and intracellular signaling with resultant mediator release. Immunologic and nonimmunologic initiation of anaphylaxis may involve other receptor activation than FcεRI receptors, such as G-protein-coupled receptors or Toll-like receptors. This type of receptor is a heptahelical transmembrane molecule that can transduce extracellular signals by way of G proteins to intracellular second messenger systems (99–102). Mast cells and basophils initiate as well as amplify the acute allergic response. Activated mast cells are regulated by a balance of positive and negative intracellular molecular events extending beyond kinases and phosphatases, such as lyn and syk kinases, which initiate a signal transduction analogous to that induced by T- and B-cell receptors. Mast-cell and basophil activation leads to rapid release of inflammatory mediators including histamine, proteases such as tryptase, mast-cell carboxypeptidase A3 and chymase, PAF, prostaglandins (PGD_2), leukotrienes, chemokines, and cytokines. In addition, stem-cell factor and its c-kit receptor are important in IgE-antigen-induced mast-cell degranulation and cytokine production. Sialic acid–binding immunoglobulin-like lectins (Siglecs) are expressed on mast cells and are inhibitory. Basophil activation, control, and involvement are not as well understood (80,103–105).

Preformed mast-cell and basophil granule mediators are released by exocytosis within minutes. Arachidonic acid metabolite synthesis occurs within minutes including prostaglandins and leukotrienes. Activation of inflammatory cytokines and chemokines takes hours. Histamine is the most important preformed and stored vasoactive mediator in mast-cell and basophil cytoplasmic granules. On its release, histamine acts on histamine receptors (H_1 > H_2) on target organs to increase vascular permeability, causing flushing, itching, urticaria, angioedema, and vasodilation with lowered peripheral resistance and shift in fluid to the extravascular space. Histamine also enhances glandular secretions causing rhinorrhea and bronchorrhea. H1 receptor activation increases mucous viscosity. H2 receptor activation increases mucous production, gastrointestinal smooth-muscle constriction, increased heart rate, and increased cardiac contraction. The heart is a shock organ in anaphylaxis as the chemical mediators act directly on the myocardium. The H1 receptors mediate coronary artery vasoconstriction and increase vascular permeability. H2 receptors increase atrial and ventricular contractile forces, atrial rate, and coronary artery vasodilation. H1 and H2 receptor interaction likely mediates decreased diastolic pressure and increased pulse pressure. PAF decreases coronary blood flow, delays atrioventricular conduction, and has depressor effects on the heart (84,106). H1 receptor stimulation may cause coronary artery vasospasm and resultant myocardial infarction even if the coronary arteries are normal. Mast-cell accumulation occurs at coronary plaque sites contributing to thrombosis. Antibodies attached to mast-cell receptors causing degranulation have potential for plaque disruption (107). Flushing, headache, increased pulse pressure, and reduced diastolic pressure are better controlled with both H1 and H2 antagonists. Pruritus may be from brain H3 receptor stimulation (106). Other preformed mast-cell mediators include neutral proteases (tryptase, chymase, carboxypeptidase A3), acid hydrolase (arylsulphatase), oxidative enzymes (superoxide, peroxidase), chemotactic factors (eosinophils, neutrophils), and proteoglycans (heparin). Along with tryptase, mast-cell kininogenase, and basophil kallikrein, activation of multiple inflammatory cascades occur in anaphylaxis. These include the contact system, clotting system, and complement system. Tryptase activation of the contact (kallikrein–kinin) system decreases high molecular weight kininogen, formation of activation complexes, and bradykinin production, causing angioedema. Tryptase can also deactivate procoagulant proteins promoting fibrin clot lysis and may lead to DIC. Chymase can activate the angiotensin system converting angiotensin I to angiotensin II to compensate intravascular volume loss from increased vascular permeability.

Released heparin (a proteoglycan) may also play a compensatory role by binding to antithrombin III inhibiting the clotting cascade as well as inhibiting the arachidonic acid cascade's generated chemoattractants for eosinophils (108,109).

Mast cells generate and release eicosanoid lipid mediators such as prostaglandins and leukotrienes. PGD_2 causes bronchoconstriction, peripheral vasodilation, and coronary and pulmonary artery vaso-constriction and inhibits platelet aggregation. PGD_2 is chemotactic for basophils, eosinophils, dendritic cells, and T_H2 cells, and it enhances histamine release from basophils. Skin mast cells mainly produce PGD_2, whereas mast cells from the lung, heart, and gastrointestinal tract secrete both PGD_2 and LTC4. Cysteinyl leukotrienes are synthesized by mast cells, basophils, and eosinophils. The cysteinyl leukotrienes stimulate smooth muscle contraction independent of histamine. They also cause mucous secretion, increased vascular permeability, arteriolar constriction, recruit inflammatory cells, modulate cytokine production, influence neural transmission, and contribute to structural changes in the airway. LTB4 is chemotactic and may contribute to the late phase of protracted anaphylaxis. PAF synthesized from membrane phospholipids causes bronchoconstriction (1,000 times more potent than histamine), increased vascular permeability, chemotaxis, and degranulation of eosinophils and neutrophils. Mast cells also release chemokines and cytokines which contribute to anaphylaxis. These mediators contribute predominately to the late phase of biphasic anaphylaxis. TNF-α is released activating neutrophils, monocyte chemotaxis, and it enhances other cytokine production by T cells. Other cytokines released include G-CSF, M-CSF, GM-CSF, IL-1, IL-3, IL-4, IL-6, IL-8, IL-10, IL-16, IL-18, and IL-22. Basophils are a major source of IL-4, IL-13, and chemokines (84,100,103,109,110).

Large quantities of nitric oxide are produced during anaphylaxis. Nitric oxide is synthesized from L-arginine through the action of nitric oxide synthase (NOS). Three isoforms of NOS exist, two constitutive (cNOS) and one inducible (iNOS). cNOS is found in endothelium, myocardium, endocardium, skeletal muscle, platelets, and neural tissue. iNOS is in macrophages, fibroblasts, neutrophils, and smooth muscle. Mediators that enhance cNOS are the same mediators of anaphylaxis: histamine, PAF, several leukotrienes, and bradykinin. Synthesis is further enhanced by hypoxia within minutes and protracted synthesis may occur over hours. Nitric oxide has the potential to be both protective (relax bronchial smooth muscle) and harmful (enhancing vascular permeability). The sum effect is detrimental with vasodilation and enhanced permeability contributing to shock (25,111).

The biphasic response, especially characterized by severe hypotension and shock, follows initial mast-cell degranulation, resulting in activation of other inflammatory cascades including the complement system and clotting and clot lysis pathways. This is supported by falls in complement and activation of clotting and clot lysis in human episodes of severe anaphylaxis (80,98). TNF-α, a preformed mast-cell mediator activates neutrophils, recruits other effector cells, and increases chemokine synthesis; it also acts like a late-phase mediator with other cytokines and chemokines contributing, in some cases, to a biphasic or protracted response (112).

The D816V KIT mutation has been identified in mast cells of patients with mastocytosis and recurrent unexplained anaphylaxis (113–116). Omalizumab, which inhibits the binding of IgE to its high-affinity receptor, FcεRI, was found to be effective for treating anaphylaxis in two patients with systemic mastocytosis (117). The association of the activating mutation in KIT with mastocytosis and anaphylaxis indicates that there might be other mutations in mast-cell signaling components that contribute to the hypersensitive phenotype and cause a predisposition to anaphylaxis (99,118).

The diagnosis of anaphylaxis is predominately clinical; however, the following findings may assist in establishing anaphylaxis as the cause of an event and establishing the potential etiology of an anaphylactic event.

A chest radiograph may show hyperinflation, atelectasis, or pulmonary edema. The most common electrographic changes other than sinus tachycardia or infarction include T-wave flattening and inversion, bundle branch blocks, supraventricular arrhythmia, and intraventricular conduction defects (11).

Other laboratory tests or oral challenges may be indicated to make a diagnosis that may mimic anaphylaxis especially in unusual cases or in ongoing management. A complete blood count may show an elevated hematocrit secondary to hemoconcentration. Blood chemistries may reveal elevated creatinine phosphokinase, troponin, aspartate aminotransferase, or lactate dehydrogenase, if myocardial damage has occurred. Acute elevation of plasma or urine histamine and serum tryptase can occur, and complement abnormalities can be observed. Plasma histamine is elevated within 5 to 10 minutes of mast-cell activation and returns to baseline within 30 to 60 minutes. This short half-life limits the reliability for anaphylaxis diagnosis unless collection occurs within 15 to 60 minutes of onset. Urinary histamine metabolites, including *N*-methylhistamine, the main metabolite of histamine whose half-life is 30 minutes, may be found for up to 24 hours after the onset of anaphylaxis, and peaking at 3

hours. Determination of plasma histamine may be more sensitive than serum tryptase, however, by the time most patients are seen, plasma histamine levels have returned to normal, thus an advantage to measure 24-hour urinary histamine metabolites rather than plasma histamine. Mast cell–derived tryptase with a half-life of several hours achieves a peak level at 60 to 90 minutes and remains elevated for up to 5 hours following anaphylaxis. Optimal times for collecting serum tryptase levels range from 15 to 180 minutes of the onset of anaphylaxis. The peak tryptase level (typically within 1 hour of anaphylaxis onset) usually correlates with the severity of symptoms, particularly with the nadir of mean arterial pressure. Larger releases of tryptase can be detected longer and have been reported to be elevated for many hours after severe anaphylaxis. Total tryptase levels can be elevated in conditions other than mastocytosis and anaphylaxis, such as acute myelocytic leukemia, hypereosinophilic syndrome associated with the F1P1 L1-PDGFRA mutation, myelodysplastic syndromes, end-stage renal disease with endogenous stem-cell factor elevation, acquired C1 esterase deficiency in association with non-Hodgkin's lymphoma, multiple trauma, asphyxia, myocardial infarction, heroine intoxication, and hypereosinophilic parasitosis (119–125). The β-tryptase level is more specific than total tryptase. The ratio of total tryptase to β-tryptase is helpful in differentiating anaphylaxis from mastocytosis. A ratio of 10 or less suggests anaphylaxis and a ratio of 20 or greater indicates mastocytosis. This differentiation is very helpful when anaphylaxis occurs in a patient with mastocytosis who has a high baseline tryptase level. In a study of patients with systemic mastocytosis who experienced anaphylaxis, it was found that mast-cell activation could be manifested by a selective excessive release of PGD_2, and these patients responded to treatment with aspirin but not to antihistamines (126). Patients with systemic mastocytosis or monoclonal mast-cell activation syndrome are at increased risk for anaphylaxis prompting obtaining a baseline and symptomatic serum tryptase level in any patient with repeated unexplained episodes of anaphylaxis.

A normal serum total tryptase does not exclude anaphylaxis. Some authors describe no relevant increase of serum tryptase during nonfatal anaphylaxis to foods and anaphylactoid reactions to vancomycin. In contrast, a rise in tryptase has been consistently observed after nonfatal insect-sting challenge. These differences might be related to the route of allergen administration. Parenteral allergen administration seems to be associated with a more pronounced increase in serum tryptase levels, possibly due to the preferential triggering of tryptase and chymase containing mast cells, which contain approximately threefold more

tryptase than human tryptase containing chymase negative mast cells (119,120,126–128). Serum tryptase may not be detected within the first 15 to 30 minutes of onset of anaphylaxis; therefore, persons with sudden fatal anaphylaxis may not have elevated tryptase in their postmortem sera. Unfortunately, even with optimal timed sampling, plasma histamine and tryptase levels remain within normal limits. If available, comparison to stored or postevent serum tryptase levels may be useful as well as serial tryptase levels.

Gill et al. (129) reviewed the role of PAF in anaphylaxis, and very high serum PAF levels correlated better than serum tryptase or histamine with anaphylaxis severity, and anaphylaxis grade significantly correlated with basal levels of PAF acetylhydrolase.

Future research may promote newer use of basophil anaphylaxis markers such as flow cytometric procedures to detect CD63, CD203c, complement system activation markers C3a-C4a-C5a, the eosinophil activation marker, and eosinophil cationic protein (89,120,124,130–133).

Future availability of measuring other mast-cell and basophil activation markers listed in an electronic medical record's particular order set as an anaphylactic panel would be useful. These could include: serum tryptase, plasma histamine, 24-hour urinary PGD_2, mast-cell carboxypeptidase A3, serum chymase, PAF, PAF acetylhydrolase activity (5,20,125,134). Serum-specific IgE antibody testing when indicated can be measured to suspected foods, venoms, and drugs on postmortem serum. The postmortem serum tryptase and the determination of specific IgE together may elucidate the cause of an unexplained death. Sera should be obtained preferably ante mortem or within 15 hours of postmortem for tryptase and specific IgE assays, with sera frozen and stored at −20°C (7,11). When evaluating postmortem blood tryptase, β-tryptase blood concentration is very high in anaphylaxis due to RCM, and less in food-related anaphylaxis. Intermediate values are obtained not only in cases of insect stings but also in cases not clearly related to allergen exposure, such as heroin-related deaths, several cases of sudden infant death syndrome, posttraumatic deaths, and in cases of heart disease. This implies difficulties of differential diagnosis, which diminish the value of blood tryptase. Systematic studies on the number of mast cells resident in healthy tissues, compared to those present in anaphylactic death cases, along with the rate of degranulation in both tissues, are required to give immunohistochemistry with anti-tryptase antibody value of anaphylaxis evidence (135–144).

The role of the spleen during anaphylaxis is important, where quantifying

eosinophils and mast cells in the spleen in combination with tryptase measurements in serum may be possible to diagnosis anaphylaxis with a higher degree of certainty. Trani et al. found splenic eosinophilia as the main feature for the differential diagnosis in four cases of antibiotic-induced anaphylaxis, recommending the use of the pagoda red stain to show the concomitant massive presence of mast cells and degranulated mast cells, mainly located in splenic sinuses, proving tryptase to be released in the blood flow (145,146).

Diagnosis and Differential Diagnosis

Criteria for the diagnosis of anaphylaxis were established by a multinational group of participants in 2014 (147). This consensus group reviewed the definitions from four different allergy immunology organizations. Having any one of the three criteria outlined in Table 14.2 is expected to capture more than 95% of the cases of anaphylaxis. More than 80% of anaphylactic episodes include skin symptoms. However, cutaneous symptoms are absent in up to 20% of anaphylaxis cases in children with food and insect-sting allergy.

Many individuals with anaphylaxis never develop hypotension or shock, an observation addressed by these criteria, supported by further defining anaphylaxis: "Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death" (2). Because of the profound and dramatic presentation, the diagnosis of anaphylaxis is usually readily apparent, especially in a medical environment where medications and diagnostic agents are administered. Rapid onset of cutaneous manifestations with concurrent respiratory complaints typically prompt rapid diagnosis and therapeutic intervention. Unless shock is present, the absence of cutaneous signs and symptoms cast doubt on the diagnosis of anaphylaxis. Other diagnoses must be considered. These include cardiac arrhythmia, myocardial infarction, other types of shock (hemorrhagic, cardiogenic, endotoxin), severe cold urticaria, hereditary angioedema accompanied by rash, aspiration of food or foreign body, insulin reaction, pulmonary embolism, seizure disorder, vasovagal (vasodepressor) reaction, hyperventilation, globus sensation, and factitious allergy—nonorganic (panic attack, Munchausen stridor-factitious anaphylaxis), vocal-cord dysfunction syndrome, undifferentiated somatoform anaphylaxis, prevarication anaphylaxis. The most common is vasodepressor collapse after an injection or a painful stimulation. This is exhibited by hypotension, pallor, weakness, diaphoresis, nausea, and occasional vomiting. The characteristic finding of bradycardia typically differentiates it from anaphylaxis; however, relative bradycardia has been reported with insect-sting anaphylaxis (148). In vasodepressor collapse,

there is no pruritus or cyanosis. Respiratory difficulty does not occur and symptoms are almost immediately reversed by recumbency and lower extremity elevation. Hereditary angioedema or acquired C1 inhibitor deficiency must be considered when laryngeal edema is accompanied by significant abdominal pain. This disorder usually has a slower onset, and lacks urticaria and hypotension. There often is a family history of similar reactions. A relative resistance to epinephrine is noteworthy.

TABLE 14.2 CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis is highly likely when any *one* of the following three criteria are fulfilled

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissues, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), *and at least one of the following*:

   a. Respiratory compromise (e.g., dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)

   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a *likely allergen for that patient* (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch–flush, swollen lips-tongue-uvula)

   b. Respiratory compromise (e.g., dyspnea, wheeze—bronchospasm, stridor, reduced PEF, hypoxemia)

   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):

   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP[a]

   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

[a]Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90

Scombroidosis and saurinosis may mimic anaphylaxis; the former is due to histamine and the latter reaction is from the histamine-like chemicals, saurine and *cis*-urocanic acid, which are bacterial by-products from spoiled fish. Flushing may also be due to carcinoid, menopause, chlorpropamide, alcohol, medullary carcinoma of the thyroid, autonomic epilepsy, vasointestinal polypeptide secreting tumors, and IA (25,149). Excessive endogenous production of histamine may mimic anaphylaxis from systemic mastocytosis, urticaria pigmentosa, basophilic leukemia, tretinoin-treated acute promyelocytic leukemia, and ruptured hydatid cyst. Other miscellaneous mimickers of anaphylaxis include paradoxical pheochromocytoma, red man syndrome (vancomycin), and capillary leak syndrome (5,25,84,149).

Munchausen stridor patients can be distracted from their vocal-cord adduction by maneuvers such as asking the patient to cough. If carried out, the cough is preceded by a nonstridorous inspiratory auscultation especially over the neck. There are no cutaneous signs. In vocal-cord dysfunction syndrome patients, the involuntary vocal-cord adduction can be confirmed by video laryngoscopy during episodes and absence of cutaneous signs (149,150). When a disorder mimicking anaphylaxis is suspected, the following laboratory testing and imaging is suggested: mastocytosis/mast-cell activating disorders (MCADs); baseline serum tryptase, 24-hour urinary histamine metabolites, urinary PGD_2, blood for 816V mutation; bone-marrow examination: carcinoid syndrome; serum serotonin, serum chromogranin A, urinary 5-hydroxyindoleacetic acid; special imaging: vasointestinal polypeptide tumor; vasointestinal polypeptide hormone, substance P, urokinase A, pancreastatin; special imaging: paradoxical pheochromocytoma; and 24-hour urinary catecholamines, serum catechols, plasma free metanephrine, special imaging.

A history of recent antigen exposure and clinical suspicion are the most important diagnostic tools used to determine that anaphylaxis is in process or has occurred. After initiation of treatment and confirmation of patient stability, obtain a detailed allergy-based history. It is imperative to obtain the circumstances surrounding the event. One must start with the time, location, and

season of the event, the sequence of complaints, and physical findings observed by the patient and individual(s) with the patient at the time of the event. Take great effort to confirm these findings by witnesses, medical personnel, photographs, and medical records. Carefully review the medical records. Work backward regarding the timing of exposure to food, drugs (prescriptions, over-the-counter, illicit, alcohol, herbal, natural remedies, and transferred/hidden/malicious), stings, activities, diagnostic/surgical procedures, recent/concurrent illness, and any past history of anaphylaxis to known allergens. Activity history in addition to food ingestion must include eating followed by exercise and medication(s) before the meal or before exercise. IgE antibody can be demonstrated *in vivo* by skin-prick testing (SPT). PT can be useful in predicting anaphylactic sensitivity to many antigens, and to confirm the cause of anaphylaxis with clinical correlation. Caution must be exercised beginning with very dilute antigens. Anaphylaxis has followed SPT with penicillin, and extracts of insects, aeroallergens, and foods. If the cause was obvious and episode was severe, SPT may offer more harm than benefit. Serum-specific IgE testing, when indicated, can be measured to suspected foods, venoms, and drugs and is particularly useful in those patients or physicians who may be fearful of skin testing or when extensive skin disease is present. Absence of specific IgE antibodies may justify a carefully observed graded oral food challenge. Serum-specific IgE antibody testing may be similarly useful on postmortem serum to identify allergens in uneaten portions of foods consumed shortly before the anaphylactic event. After fatal anaphylaxis, necroscopic procedures can be useful to verify and sample all materials present inside the gastric or intestinal cavities in subjects with a suspected or known diagnosis allergy to foods or drugs. Samples of blood, bile, and urine should be taken for identification, as should the names or dosage of drugs taken. When anaphylaxis is suspected due to hymenoptera or other insect stings, it could be useful to examine the skin and mucosa more carefully, if possible for a sting. When a sting is found, an entomologist may assist to identify the type of insect responsible. When death occurs from anaphylaxis without medical intervention or witnesses, the location of the event may add insight to the cause: home, workplace, field, farm, or forest. Foods, as well as the objects at the scene and near the corpse as well as the subject's clothes, must be carefully examined. Brightly colored clothes and perfumes may suggest an insect sting. All biologic or inorganic stains and tracks must be observed and sampled. Parents, relatives, or other witnesses must be interviewed. The place, month, season, and the presence of insects (one or more insects alive or dead) at the scene must be taken into account. Special attention should be paid when the scene investigations involve the corpse of a beekeeper.

Sometimes death occurs outside a hospital, during medical transport or during a hospital admission. All medical records available on clinical conditions, drugs administered, and therapeutic procedures must be reviewed. Medical personnel and other witnesses must be interviewed (151). An assay for serum tryptase may be useful, particularly in the early postmortem period, but it should not be relied upon as the sole criterion for diagnosis with limitations enumerated earlier. The utility of a total serum IgE as a confirmatory test is limited by variation within the atopic population and described elevations in the setting of trauma, sepsis, and other nonatopic conditions. Specific IgE assays may provide helpful information, particularly if the offending allergen is known or suspected and if a commercially prepared specific allergen extract is available. If fatal anaphylaxis from food is suspected, leftover or vomited food may be a useful source of antigen for an *in vitro* IgE-specific assay. Panels of candidate antigens may also provide useful clinically correlative information (120).

Other *in vitro* techniques that have been explored include the release of histamine from basophils of sensitive individuals on antigen challenge, and the ability of a patient's serum to passively sensitize normal tissues such as leukocytes for subsequent antigen-induced release of mediators (17). The only current reliable test for agents that alter arachidonic acid metabolism such as aspirin and other NSAIDs and other suspected non–IgE-mediated agents is carefully graded oral challenge with close clinical observation and measurement of pulmonary function, nasal patency, and vital signs, following informed patient consent. Substances that can directly release histamine from mast cells and basophils may be identified *in vitro* using washed human leukocytes or by *in vivo* skin testing. These agents must release histamine in the absence of IgG or IgE antibody (1,2).

The basophil activation test (BAT) is a flow cytometry-based assay in which the expression of activation markers on the surface of basophils is measured following stimulation with an allergen. The BAT has been validated in IgE-mediated conditions, including food allergies, venom hypersensitivity, and pollen allergies. The use of BAT use as a diagnostic tool in patients with life-threatening anaphylaxis from a drug, where drug provocation is not advisable, may benefit from this test, especially with simultaneous measurement of CD63 and CD203c (152–154).

▪ FACTORS INCREASING THE SEVERITY OF ANAPHYLAXIS OR INTERFERING WITH

TREATMENT

There are many factors that increase the severity of anaphylaxis or interfere with treatment (Table 14.3). Rapid intravenous infusion of an allergen in a patient with a preexisting cardiac disorder may increase the risk for severe anaphylaxis. Concomitant therapy with β-adrenergic antagonist drugs or the presence of asthma exacerbates the responses of the airways in anaphylaxis, impedes epinephrine response, and inhibits resuscitative efforts (155,156). Epinephrine use in patients on β-adrenergic antagonists may theoretically induce unopposed α-adrenergic effects, resulting in severe hypertension, however, profound shock is more likely to be caused by severe anaphylaxis. Individuals taking β-adrenergic antagonists orally or topically may experience severe anaphylaxis associated with paradoxical bradycardia, profound hypotension, and severe bronchospasm. β-adrenergic antagonists should be used with caution, and preferably avoided in patients receiving IT and for patients with IA, exercise-induced anaphylaxis (EIA), and food/drug dependent EIA. The difficulty in reversing anaphylaxis may occur in part from underlying cardiac disease for which β-adrenergic antagonists have been given. Both β1 and β2 antagonists may inhibit the β-adrenergic receptor (155). Most patients on β-adrenergic antagonists are typically not completely blocked and epinephrine therapy should not be withheld.

TABLE 14.3 FACTORS THAT INTENSIFY ANAPHYLAXIS OR INTERFERE WITH TREATMENT

Presence of asthma, undertreated asthma patient on immunotherapy

Atopy

Mastocytosis

Cardiovascular disease, especially with rapid infusion of allergen

Probable chronic renal and pulmonary disease

Age: elderly, infants, teenagers ("risky behavior")

Concomitant therapy with:

    β-adrenergic antagonist drugs

    Angiotensin converting enzyme inhibitors (ACE-I), ACE-I+β-adrenergic antagonist drugs

    Angiotensin receptor blockers

Proton pump inhibitors
Monoamine oxidase inhibitors
Tricyclic antidepressants
Alcohol
Delay or inadequate dose of epinephrine administration
Psychiatric disease

Increased vascular permeability during anaphylaxis may result in a 50% shift of intravascular fluid into the extravascular space within 10 minutes. This shift in effective blood volume activates the rennin–angiotensin–aldosterone system causing a compensatory angiotensin II and catecholamine response. ACEi and angiotensin receptor blockers (ARBs) may prevent or inhibit this response. These drugs separately can cause life-threatening tongue or pharyngeal edema (85,157,158). A review of a German anaphylaxis database and a murine model suggested the combined use of β-blockers and ACEi significantly increases the risk for severe anaphylaxis (26). ACEi may (evidence to the contrary exist) be a risk factor for an increase in incidence and severity of anaphylaxis to hymenoptera stings and venom IT (159–163). Monoamine oxidase inhibitors can increase the hazards of epinephrine by interfering with its degradation (11).

Proton pump inhibitors (PPIs) have been linked with drug-induced anaphylaxis in hospitalized patients, possibly by interfering with digestion and prolonging allergenic protein exposure during gastric transit (164).

Systemic reactions may occur more frequently in undertreated asthma patients receiving IT. Though not a standard practice, it has been recommended that measurements of FEV_1 be performed before IT, with injections withheld if FEV_1 is $\leq 70\%$ of the predicted volume (165).

CAUSES OF ANAPHYLAXIS

Many substances have been reported to cause anaphylaxis in humans. Any agent that can activate mast cells or basophils has the potential to trigger anaphylaxis. Antigens are subdivided into proteins, polysaccharides, and haptens. A hapten is a low-molecular-weight organic compound that becomes antigenic when it or one of its metabolites forms a stable bond with a host protein. With penicillin,

both the parent hapten and nonenzymatic transformation products may form bonds with host proteins to form an antigen. In cetuximab anaphylaxis patients, specific IgE has been demonstrated for the carbohydrate galactose-α-1,3-galactose, expressed in the cell line to produce this biologic agent (12). Specific IgE to galactose-α-1,3-galactose is also associated with delayed anaphylaxis to red meat from animals that carry this oligosaccharide (166).

The route of agent exposure causing human anaphylaxis may be oral, parenteral, topical, or inhalational. An example of an agent that can cause anaphylaxis by any of these four ways of entry is penicillin. The most common causes of anaphylaxis are foods, medications, insect stings, and allergen IT injections. Drugs can cause IgE- and non-IgE-mediated anaphylaxis. Previous drug exposure is required for formation of IgE; however, non-IgE-drug-induced anaphylaxis may happen on first exposure. IA is common, accounting for an estimated one-third of anaphylaxis cases (3,5,167,168). Table 14.1 lists some common causes and mechanisms of anaphylaxis. The following discussion is a review of some important and interesting causes of anaphylaxis.

Anaphylaxis Related to Drugs, Diagnostic and Biologic Agents, and Chemotherapy

Drugs, chemotherapy agents, and biologicals, including monoclonal antibodies (MoAbs), are the most common causes of anaphylaxis in health-care environments. Medication anaphylaxis is most commonly IgE-mediated, however, other non-IgE and non-immunologic mechanisms also play a role (169). IgE-specific antibodies occur from a preceding sensitization to the drug or a cross-reacting compound. Low-molecular-weight compounds may bind to serum or tissue carrier proteins and become a multivalent antigen. A parent drug's metabolites covalently bind to host proteins and induce IgE antibody production. This limits the knowledge of relevant metabolites and allergenic determinants for skin testing and *in vitro* analysis. The most common class of drugs causing anaphylaxis are the antibiotics, primarily the β-lactam antibiotics. Penicillin is the most common cause of drug-induced anaphylaxis. Cephalosporins share with penicillin a common β-lactam ring and are also a frequent cause of anaphylaxis. Cross-reactivity between penicillin and cephalosporins range from 3% to 18% of patients with previous penicillin allergy (168). Estimates of nonfatal penicillin allergic reactions vary, ranging from 0.7% to 10%, and fatal reactions are estimated at a frequency of 0.002%, or one fatality per 7.5 million injections, and one per 50,000 to 100,000 penicillin courses (170). Penicillin degrades into two main reactive intermediates termed

"major" and "minor antigenic determinants." The major determinate, benzylpenicilloyl polylysine, is commercially available as Pre-Pen (AllerQuest LLC) for skin testing. Selected universities prepare minor determinates for skin testing; penicillin G can also be used as a surrogate for the minor determinant allergens. Minor determinant sensitivity, in some patients, is associated with more severe anaphylaxis. The patient's history is a poor predictor of risk of true penicillin allergy, with 90% of patients with a history of penicillin allergy having negative penicillin skin tests tolerating penicillin (171). The positive predictive value of penicillin skin testing is 97% to 99%.

Only a small percentage of positive penicillin history patients with a positive penicillin skin test have adverse allergic events when administered cephalosporin. Anaphylactic deaths have occurred in individuals allergic to penicillin, who were not skin tested and administered a cephalosporin antibiotic. Patients who have a penicillin allergy history and negative penicillin skin tests to major and minor determinants are at no greater risk and may receive cephalosporins, though cautious graded challenges are typically performed. Monobactam antibiotics such as aztreonam do not cross-react with penicillin or other β-lactams, except ceftazidime. Skin-test studies suggest cross-reactivity between carbapenems and penicillin, necessitating penicillin skin testing before considering administration of carbapenems. However, the rate of clinical reactions in penicillin skin test–positive patients is much lower than anticipated, suggesting a low rate of cross-reactivity. In patients with non–IgE-mediated penicillin allergy, such as Stevens–Johnson syndrome or toxic epidermal necrolysis, penicillin skin testing should not be performed because penicillin is almost strictly contraindicated. Anaphylaxis to non-β-lactam antibiotics is less common. Skin testing using a nonirritating concentration of the parent drug at times may yield useful information; however, the predictive value is uncertain. Unfortunately, this limits the diagnosis to the patient's history (172,173).

Aspirin and other NSAIDs are the second most common cause of drug-induced anaphylaxis. Anaphylaxis from these agents is thought to be agent-specific, with patients tolerating other NSAIDs (174). The cause is unknown with lack of drug-specific IgE detection by skin and *in vitro* testing, and a disturbance of arachidonic acid metabolism is suspected. Caution is advised if administering nonselective NSAIDs; COX-2 antagonists are usually tolerated.

Anaphylaxis to anticancer drugs has become more frequent and most commonly include platins, taxenes, doxorubicin, asparaginase, and epipodophyllotoxins. With the growing variety of cancers, platins are being used

for prolonged periods and number of platin exposures is a risk factor for platin anaphylaxis. The most commonly used platins include carboplatin, cisplatin, and oxaliplatin (175–177). Skin testing to some of the anticancer drugs may be helpful in determining whether sensitivity exists, and what dose to proceed with if desensitization is required. Anaphylactoid infusion-related reactions occur in up to 30% of patients upon first exposure, which may necessitate for future infusions "desensitization," premedication, and infusion rate reduction. The solvent vehicle in which drugs are formulated may cause anaphylaxis, such as with Cremophor EL use with paclitaxel. Components other than the drug product intended to use may be the culprit, e.g., heparin contaminated with oversulfated chondroitin sulfate (18,178–185).

Anaphylaxis occurs from biologic modifiers and monoclonal antibodies. Biologic modifiers and monoclonal antibodies are being introduced into the drug market at an increasing rate. This recent emergence has not allowed an estimated incidence of anaphylaxis. The use of omalizumab (anti-IgE), a recombinant humanized murine anti-IgE antibody, is therapeutic for severe allergic asthma and chronic urticaria. The rate of anaphylaxis from omalizumab is estimated between 0.09% and ≤0.2%. Anaphylaxis occurred in 48 cases from an estimated 39,510 omalizumab-exposed patients. Anaphylaxis can occur after any dose, even if a previous dose was well tolerated. Anaphylaxis occurred after the first dose in 40% of cases and after repeat administration in 56% of cases. Some patients experienced anaphylaxis after 2 years of chronic treatment. Anaphylaxis occurred within 2 hours in 71% of cases with delayed onset between 2 hours and >24 hours after injection. Omalizumab-induced anaphylaxis is generally delayed with a protracted progression of symptoms. This has prompted the recommendations that patients should be observed for 2 hours after the first three injections and 30 minutes after subsequent injections and be administered at a facility that has appropriate staff and equipment to treat anaphylaxis, with availability of auto-injectable epinephrine with the patient. Anaphylaxis has been reported to many other biologics, and patients can be successfully desensitized if necessary after anaphylaxis. Biologics have a larger molecular weight compared to other drugs, which are haptens, and skin testing reactions have been shown to be positive in most patients with allergic reactions to rituximab, infliximab, and trastuzumab, who underwent desensitization. Skin testing should be considered in the evaluation of patients with anaphylaxis to biologics in preparation to treat with desensitization or an induction of tolerance. Patients with negative skin tests can still have reactions during desensitization and attempts to induce tolerance (12,13,186–196).

Monoclonal antibody reactions also induce infusion reactions resulting from cytokine release and/or immune complex generation. These reactions occur with the first or second exposure, are more frequently seen with murine monoclonal antibodies, and are characterized by rigors, fever, joint pain, and hypotension in severe cases. Because chimeric, humanized, and human monoclonal antibodies have been engineered with less immunogenic potential, the frequency of these reactions has decreased (197).

RCM is estimated to cause one death in every 75,000 patients who are exposed to it. The overall frequency of adverse events is 5% to 8%; moderate reactions that require therapy occur in 1% of patients that receive RCM. Life-threatening reactions occur with a frequency of <0.1% associated with high-osmolality RCM, and decreased to one-fifth less with low-osmolality RCM. Risk factors for an RCM reaction include a previous reaction to RCM (risk 16% to 44%), a history of cardiac disease, asthma, chronic kidney disease, β-blocker use, food allergy, drug allergy, contact allergy, and therapy with cytokine IL-2. Neither seafood allergy nor allergy to iodine is a risk factor for RCM anaphylaxis. Pretreatment to prevent an anaphylactoid reaction in a patient who must receive RCM is 50 mg of prednisone orally 13, 7, and 1 hours before administration of RCM and 50 mg diphenhydramine orally or intramuscularly 1 hour before the administration of RCM. If the patient requires emergency RCM, administer 200 mg hydrocortisone intravenously, and then every 4 hours until the RCM is administered, and 50 mg diphenhydramine 1 hour before RCM administration (198–206).

In summary, medications can potentially trigger anaphylaxis through an IgE-dependent immunologic mechanism (β-lactam antibiotics), an IgE-independent immunologic mechanism (high-molecular-weight iron dextran, infliximab), or direct mast-cell stimulation (opioids). Biologic agents that induce anaphylaxis through an IgE-dependent immunologic mechanism include mono-clonal antibodies (cetuximab and omalizumab), allergens used in IT, and vaccines (more commonly from its protein excipient, such as gelatin or egg, than the actual immunizing agent). A medication may be a co-trigger of anaphylaxis, such as with NSAIDs and EIA. Contaminants in medications may induce anaphylaxis, such as oversulfated chondroitin sulfate in heparin. RCM potentially triggers anaphylaxis through an IgE-dependent immunologic mechanism or through activation of complement (24,183).

Insect Stings and Bites

Insect stings are well known to cause anaphylaxis, but such reactions are rare with biting insects. The most common are from venom from members of the order Hymenoptera: yellow jackets, hornets, bees, wasps, fire ants, and harvester ants. Less commonly implicated is from insects' saliva including the Triatoma—kissing bugs or assassin bugs as well as from flies, mosquitoes, ticks, and caterpillars. Systemic allergic reactions to insect stings occur in an estimated 3.3% of the population (3% adults and 1% children) and an estimated 40 deaths occur annually in the United States from hymenoptera stings. Hymenoptera stings have an incidence of 23 deaths per 150 million stings. The National Office of Vital Statistics estimated an average death rate of 0.28 per 1 million persons per year from hymenoptera stings. Fire-ant stings also cause human anaphylaxis, particularly in the southern United States, at an estimated annual rate of 0.6% to 16%, with >80 fatalities. Victims may not accurately identify the specific insect necessitating confirmation of hypersensitivity by skin testing with purified venoms or whole-body fire-ant extracts. *In vitro* tests for venom-specific IgE antibodies can be used to confirm a clinical history of hymenoptera or fire-ant hypersensitivity. Systemic reactions are not always progressively more severe with each sting. Children with a history of moderate or severe anaphylaxis to stings who did not receive venom IT still had a 32% frequency of anaphylaxis to recent stings. In adults who have had a previous systemic reaction to stings, a repeat sting causes another systemic reaction in 30% to 65% of cases, depending mainly on the severity of previous reactions, the level of venom sensitivity, and the species of insect. Severe reactions to insect stings with confirmed positive venom-specific IgE skin or serum tests warrant the physician to advise highly effective hymenoptera venom or whole-body fire-ant extract IT. Additionally, the patient should carry auto-injectable epinephrine and practice avoidance measures (207–212).

Food

In the United States, an estimated 150 food-allergy-related deaths occur each year. In food-related fatalities reported by Bock, 87% of the subjects had a previous history of a reaction to the responsible food (213). Food is the leading cause of outpatient anaphylaxis accounting for one-third to one-half of anaphylaxis visits to emergency departments in North America, Europe, Asia, and Australia (214). Any food may cause anaphylaxis, but certain foods are more commonly associated with severe reactions. Peanut, tree nuts, and seafood represent the most frequent food triggers of anaphylaxis among children and adults. For younger children, cow's milk and eggs are the most common trigger.

In this group, cow's milk has been reported to account for up to 13% of fatal food-induced anaphylaxis. Although 75% of children with cow-milk allergy tolerate milk in baked forms, and children who are reactive to baked milk have been found to have a higher risk of severe and protracted anaphylaxis requiring epinephrine (213,215,216). During adulthood, the most common food-induced anaphylaxis occurs from peanuts, tree nuts, fish, and shellfish (217). Dietary factors within particular geographical regions affect the prevalence of food allergy. Peanut allergy is the most common food allergy in the United States, with seafood in Hong Kong and sesame in Israel (45). There are other geographic variations in the predominate food that may cause anaphylaxis including chestnut, rice, buckwheat, and chickpea. The food trigger may not always be obvious, such as hidden, trace, malicious, or cross-contaminating food in a meal or snack. Other potential triggers may include hormonally or genetically modified food, substituted food, a hidden food ingredient, food additive (spices, vegetable gum), or food colorant (carmine). The α-gal allergen present in beef, pork, and lamb may trigger late-onset anaphylaxis in individuals with preexisting IgE to galactose-α-1,3 galactose, sensitized by a previous bite from a lone star tick (24,218,219). Lipid transfer protein (LTP) is a panallergen found in plants and is resistant to heat and pepsin digestion. LTP is found in many fruits and vegetables, some grains, as well as peanuts and tree nuts, and it has been implicated as a common cause of food-induced anaphylaxis and food-dependent EIA (220–222).

Food-induced anaphylaxis most frequently occurs at home with nearly one-fifth cases at school. In a UK study of 202 anaphylactic deaths, 45 (30%) were from food. Over 50% were attributable to nuts; 33% occurred at home, 25% at restaurants, and 15% at work or school. Food-induced anaphylaxis onset can occur within seconds to a few hours after ingestion. Fatalities may occur within 30 minutes (88,223,224).

Diagnostic confirmation of food-induced anaphylaxis can be challenging. A lack of serum tryptase elevation occurs in the majority of cases (77). This may be due to basophil as opposed to mast-cell mediation, as well as slower or biphasic onset. Decreased activity, or deficiency, of PAF acetylhydrolase, the enzyme that inactivates PAF, has been described as a risk factor for severe and fatal anaphylaxis from foods. A better marker for food-induced anaphylaxis may be serum levels of PAF acetylhydrolase activity (PAF-AH) and mast-cell carboxypeptidase (77,215). If the cause of anaphylaxis is not apparent from the patient's history (ingredient list from package/manufacture/recipe/chef), IgE-specific skin testing with food extracts or checking for serum food-specific IgE

antibodies may reveal the food responsible (225). Food selection for skin prick or *in vitro* testing must be guided by the patient's history because up to 60% of the general population has food sensitization of which the majority will not develop anaphylaxis. Intradermal food testing is contraindicated. Not all commercial food allergens are standardized, frequently necessitating SPT with fresh foods.

Skin testing with foods, rarely, may cause anaphylaxis, necessitating the use of diluted solutions, the skin-prick technique, physician's presence, not necessarily applying all suspected foods simultaneously, and availability of emergency medications and equipment. Food-specific IgE levels with >95% predictive risk values for clinical reactivity by food-specific IgE antibodies have been defined for adults as follows: cow's milk $\geq$ 15 kU/L, egg $\geq$ 7 kU/L, peanut $\geq$ 14 kU/L, tree nuts $\geq$ 15 kU/L, and fish $\geq$ 20 kU/L; for infants, the levels are: cow's milk $\geq$ 5 kU/L and egg $\geq$ 2 kU/L. The rate of decrease in food-specific IgE levels over time also has predictive value. Panels of food allergen testing are not recommended because they can result in false-positive testing and unnecessary dietary restriction. Oral food challenges are most often used to eliminate incriminated foods that are highly unlikely to have caused the event or to document tolerance to a past food which caused anaphylaxis following years of abstinence and lack of sensitization by IgE testing. Physician-monitored graded oral food challenge in an emergency-equipped environment is, at times, required to exclude anaphylaxis. These challenges are time consuming, are not without risk, and should be guided by follow-up measurements of specific IgE-levels and SPT. In those who tolerate double-blind placebo-controlled food challenges, recurrence of allergy occurs in 8% of peanut allergic individuals. This risk may be elevated when peanut is avoided after a negative challenge, suggesting regular consumption is necessary to maintain peanut tolerance. Other testing modalities are becoming standardized, such as component-resolved diagnostics (CRD), which measure serum IgE to specific allergen epitopes in serum via an automated microarray and the BAT, which involves flow cytometry to detect upregulation of cell surface markers on the basophil, such as CD63, after *in vitro* antigen stimulation of blood, both of which may also predict severity of reactions. BAT might offer a way to distinguish patients who have developed tolerance to a food allergen. CRD testing in food-induced anaphylaxis, just like skin tests or measuring specific serum IgE to an allergen, is able to assess only sensitization and not clinical reactivity (20,40,215,226–230).

Latex Anaphylaxis

Between 1988 and 1992, the U.S. Food and Drug Administration received more than 1,000 reports of latex anaphylaxis, 15 of which were fatal (231). Many efforts have been made in the past 10 years to reduce both latex exposure and sensitization by decreasing the protein content and stopping the use of powdered gloves, resulting in a marked decrease of the number of reactions to latex in several countries (232). Latex sensitivity and latex-related symptoms, such as urticaria, pruritus, asthma, and rhino-conjunctivitis, have reduced in health-care workers because of the use of low-protein, powder-free gloves instead of high-protein powdered gloves (233). The prevalence of latex allergy is dependent on the population studied and ranges from 3% to 64%. Latex sensitization in the general population varies from 5.4% to 7.6%. Repeated contact with or prolonged exposure to latex-containing products may result in adverse latex reactions. Patients with spina bifida or urogenital abnormalities are a particular subpopulation at risk with a prevalence of >60% due to multiple surgeries early in life, resulting in frequent latex exposure. Approximately 10% to 20% of health-care workers are sensitized to latex. Exposure to rubber gloves is a frequent cause of occupational latex allergy, but contact with other types of latex-containing articles both in the medical and nonmedical settings may also play a role. Workers in the latex manufacturing industry are another subpopulation at risk (234). In the community, anaphylaxis is still occasionally reported after direct exposure to latex gloves, condoms, rubber-handled racquets, balloons, latex-padded play pits, infant pacifiers, and bottle nipples (24). It can also occur after ingestion of foods that cross-react with latex, the so-called latex-fruit syndrome, such as banana, kiwi, papaya, avocado, potato, and tomato. CRD-associated molecules include Hev b2, Hev b 5, Hev b 6.02, Hev b 7, and Hev b 13 (24,230). People rarely react to hard-extruded rubber products such as automobile tires (235). Risk factors for health-care workers include a personal history of atopy, frequent use of disposable latex gloves, and hand dermatitis (236). Clinical differences have been observed between surgical and nonsurgical latex-induced anaphylaxis. Cutaneous, respiratory, and cardiovascular manifestations can occur in both. Cardiovascular collapse is a feature of surgical procedures, with dizziness or syncope more frequent in nonsurgical procedures. IgE detection by skin tests are more sensitive than measuring serum latex-specific IgE antibodies, which are highly variable and sensitive (sensitivity 50% to 100%). No approved latex skin-test reagent is available in the United States. Extracts have been made from raw latex (sap) and latex glove extracts (allergen content highly variable). Systemic reactions to latex skin testing have been reported; thus, care must be exercised when skin testing with uncharacterized extracts (237). CRD can be useful where monosensitization to cross-reactive

carbohydrate determinants occur or to (*Hevea brasiliensis*—Hev), Hev b 8 (profilin) suggesting nonrelevant sensitization, whereas markers of genuine allergy, including anaphylaxis, are Hev b 1, Hev b3, Hev b 5, and Hev b 6 (230). When a patient tests positive for latex-specific IgE with a history of latex anaphylaxis, the patient and medical record must be labeled as latex allergic. Latex must be avoided by these individuals, and when in the hospital, a latex-free environment should be provided. There is currently no cure for latex allergy, and avoidance of latex-containing products is mandatory for affected individuals (234). Inadvertent exposure may occur necessitating carrying of auto-injectable epinephrine.

Anaphylaxis during Immunotherapy

Fatalities from allergen IT and skin testing are rare, with 24 fatalities (1:2.8 million injections) from IT reported between 1959 and 1984 (238). In another study, 17 fatalities (1:2 million injections) associated with IT occurred from 1985 to 1989 (239). In 2004, Bernstein et al. identified 41 IT fatalities spanning a 12-year period (1990 to 2001) or an average of 3.4 fatal IT reactions per year and a fatality rate of 1 per 2.5 million injections (240). Nonfatal anaphylaxis is estimated to occur at the rate of one event per 1 million injections with a rate approximately 2.5 times greater than that of fatal anaphylaxis (241). Fatal anaphylaxis from IT occurs with greater frequency among patients with severe or poorly controlled asthma, if the IT is administered outside the prescribing allergist's office, during the IT build-up phase, on patients with history of prior systemic reaction from IT, with errors in dosing and administration, or when administering IT during a patient's peak allergen season (238–242). Fatality due to skin testing is extremely rare with six reported deaths from intradermal testing; all but one patient was asthmatic (238). There was one reported death from percutaneous testing with 90 commercial food extracts (240).

Perioperative Anaphylaxis

Perioperative anaphylaxis occurs mainly in adults, typically follows anesthetic induction, and may be either immune (usually IgE-mediated, sometimes IgG-mediated) or nonimmune in etiology. The incidence of anaphylactic reactions during anesthesia varies between countries, ranging from 1/1,250 to 1/18,600 per procedure. Although these reactions occur in a monitored setting, death may be the outcome even when anaphylaxis is rapidly recognized and appropriately treated. The proportion of IgE-mediated allergic reactions is similar between countries, ranging from 50% to 60%. Significant geographical variability

regarding different drugs or substances involved is reported. Antibiotics are likely the most common cause of perioperative anaphylaxis in the United States (approximately 50% of cases), whereas neuromuscular blocking agents are the most common suspected cause in Europe (approximately 70% cases). Reactions involving antibiotics, dyes, or chlorhexidine are reported with a higher and sometimes increasing frequency in most series. Reactions to latex are rapidly decreasing as a result of prevention policies. Regional differences support the need for repeated epidemiologic surveys in different countries (5,232). Perioperative anaphylaxis incidence may range from 1:10,000 to 1:20,000 administrations. The reported incidence variance is related to the difficulty in identifying the total number of drugs administered and the challenge in recognizing perianesthetic hypersensitivity reactions. In general, greater risk is associated with general anesthesia compared with local or spinal anesthesia (243,244). Perioperative anaphylaxis typically occurs within minutes of anesthetic induction and is primarily linked to intravenously administered drugs. The more rapidly the immediate reaction occurs after drug exposure, the more likely the reaction will be life-threatening. NMBAs and antibiotics (primarily β-lactam drugs) are the main causes. Anaphylaxis to sedative-hypnotic drugs, opioids, and amide local anesthetics is rarely reported. Anaphylaxis may also occur during the maintenance phase of anesthesia or the recovery period. Dyes (patent blue V and its derivative isosulfan blue, methylene blue), colloids (modified fluid gelatins, starch solutions), antiseptics (chlorhexidine, povidine iodine), RCM, and aprotinin (some fibrin glues containing aprotinin) may be involved (244–246).

NMBAs are an important cause of anaphylaxis during anesthesia. Rocuronium and succinylcholine are the most commonly reported agents (5,101, 102, 247–252). The mechanism may be IgE-mediated, pseudoallergic, or from direct histamine release from mast cells (5,253). NMBAs IgE recognition site involves the substituted ammonium ions and explains the frequent cross-reactivity between the different NMBAs. Cross-reactivity to all NMBAs is unusual, and is more frequent with aminosteroid NMBAs than with benzylisoquinoline-derived NMBAs. Cross-reactivity occurs most commonly between vecuronium and pancuronium. Succinylcholine and rocuronium have a higher risk of anaphylaxis than pancuronium and *cis*-atracurium. First-exposure anaphylaxis to NMBAs suggests environmental factors playing a role in cross-sensitizing patients against NMBAs. A possible sensitization likely results from previous exposure to compounds containing tertiary and/or quaternary ammonium groups, such as cosmetics or disinfectants. Reactions are more

common in women, and it is thought that cross-reactivity of specific IgE with NMBAs can occur with the ammonium compound found in personal-care products (5,248). A study conducted on hair dressers demonstrated a significant increase in IgE-sensitization to NMBAs and quaternary ammonium-ion compounds (254). The management plan for patients who experienced a documented NMBA-induced anaphylaxis and needed NMBA for future procedures is solely based on skin testing. NMBA cross-reactivity is identified by skin testing, and negative skin-tested NMBAs are used for subsequent anesthetics. The patterns of cross-reactivity between NMBAs vary considerably and are dependent on each patient. Identification of serum IgE provides possible evidence of IgE sensitization. However, by itself, it does not confirm that the drug induces the immediate reaction and is not predictive of the clinical outcome (249,255–258).

The most common antibiotics associated with perioperative anaphylaxis include the β-lactams and vancomycin. The highest cross-reactivity occurs between the penicillin and first-generation cephalosporin, with an increase in anaphylaxis reported from the increased use of perioperative antibiotic prophylaxis. IgE-mediated anaphylaxis has been reported from vancomycin, however, more commonly seen is vancomycin-induced red man syndrome caused by direct histamine release from mast cells, which is infusion-rate-dependent. IgE-mediated anaphylaxis has also been reported to fluoroquinolones, rifampin, and bacitracin. Guidelines recommend that infusion of antibiotics should be carried out when the patient is awake in order to assess any developing untoward allergic event in a better way (247,253,259–263).

Hypnotics, such as the barbiturates, particularly thiopental, may cause anaphylaxis. Specific IgE antibody and direct histamine release have been implicated as the mechanisms of action. These reactions are more common in women. Reaction to etomidate and ketamine are rare. Propofol has been reported to cause IgE-mediated reactions due to its two isopropyl groups acting as antigenic epitopes; however, most reactions are secondary to direct histamine release. There is no evidence to support the theory that patients allergic to egg and soy have an increased risk of anaphylaxis to propofol (41,247–249,252,253,264–269). Intravenous diazepam allergy is likely caused by thepropylene glycol solvent, which is sensitizing and can be found in other medications, cosmetics, vaccine, and foods. IgE to its metabolite has been proposed to be responsible for its cross-reactivity with other benzodiazepines (248,269).

Narcotics rarely cause anaphylaxis in the perioperative period, more commonly causing flushing, urticaria, pruritus, and mild hypotension, which are lessened by reducing the intravenous rate. Although fentanyl has not been shown to stimulate histamine release, there are reports of IgE-mediated anaphylaxis to morphine and fentanyl. Narcotics, with the exception of fentanyl, cause direct release of mast-cell mediators (5,248,253,270–273).

Colloids or plasma expanders, such as dextrans, hydroxyethyl starch (HES), gelatin, and albumin, are responsible for anaphylaxis at rates of 4% of all perioperative anaphylaxis, 0.008% to 0.08% for dextran, and 0.08% for HES. The clinical significance of reported specific antibodies to dextran and HES is unknown. Specific IgE antibodies have been detected to gelatin. Gelatin is contained in many products including foods, vaccines, pharmaceuticals, and cosmetics, potentially allowing sensitization. Anaphylaxis to albumin has been reported; the mechanism is unclear (5,248,274–287).

Blood transfusion reactions may be hemolytic from complement activation or from anti-IgA antibodies in an IgA-deficient patient receiving IgA antibody in nonwashed packed red blood cells or whole blood from a normal donor. These anti-IgA antibodies typically are IgG; some may be an IgE isotype (288). The hemostatics protamine, aprotinin, and thrombin can cause anaphylaxis with IgG and IgE antibodies identified. Anaphylaxis to fibrin sealants have also been reported. There may be fish cross-reactivity with protamine (5,289–292). See more on blood product induced anaphylaxis subsequently.

Other agents reported to cause perioperative anaphylaxis include NSAIDs (non-IgE, possible IgE), ACEi (non-IgE mediated), local anesthetics (rare, 97% negative skin tests), chlorhexidine (IgE), blue dyes (possible hapten induced IgE), and RCM (non-IgE, IgE, immediate and late). Risk factors for an RCM reaction include a previous reaction to RCM, a history of cardiac disease, asthma, chronic kidney disease, β-blocker use, food allergy, drug allergy, contact allergy, and therapy with cytokine IL-2 (5,248,249,270,293–300).

The most commonly implicated drug hypersensitivity reactions in patients with mastocytosis are opioids, NSAIDs, and NMBAs, and perioperative anaphylaxis may be the presenting manifestation (169).

Perioperative anaphylaxis requires an evaluation by an anesthesiologist along with an allergist to carefully evaluate the medical and anesthetic record. This includes a presurgical evaluation for patients with known previous perioperative anaphylaxis and post perioperative anaphylaxis evaluation obtaining appropriate biomarkers of anaphylaxis, such as a serum tryptase and plasma histamine level,

and skin prick and, if appropriate, intracutaneous testing to suspected agents at 4 to 6 weeks after the event. The 4- to 6-week delay is to ensure that mast cells and basophils are not refractory to activation. Mertes and colleagues published skin testing guidelines with nonirritating concentrations of commonly used NMBAs, hypnotics, opioids, local anesthetics, chlorhexidine, and methylene blue. Identification of serum IgE provides possible evidence of IgE sensitization, and by itself does not confirm that the drug induced the immediate reaction. Other *in vitro* tests are available, however, they are less sensitive and specific when compared to skin testing and are not always readily available. These include specific serum IgE measurement to the tertiary or quaternary ammonium groups of NMBAs, to β-lactam antibiotics, morphine, chlorhexidine, protamine, and latex. Identification of serum IgE indicates possible IgE sensitization, but by itself, it does not constitute proof that the drug induced the anaphylaxis. The result should always be correlated with the clinical history (5,242,245,247,249,253,256–258,301–308).

Blood Components and Seminal Fluid

Blood transfusions induce anaphylaxis through several mechanisms. These include: cytotoxic reactions from IgG or IgM antibodies, inadvertent transfusion of small amounts of IgA to IgA-deficient patients, and passive transfusion of IgE antibodies from allergic donors transiently sensitizing recipients' mast cells and basophils. An estimated 25% of blood donors have IgE antibodies to common allergens and an estimated one-third of these donors have allergen-specific IgE > 10 kU/L. A nonatopic recipient may be passively sensitized by transfusion of donor blood containing elevated titers of IgE. Conversely, in rare cases, transfusion of an allergen (e.g., peanut) or drug into an atopic recipient has caused plasma anaphylaxis (24,309).

Antihuman IgA antibodies are present in about 40% of individuals with selective IgA deficiency. Very rarely, there have been reports of allergic reactions varying from mild urticaria to fatal anaphylaxis, typically following numerous transfusions. These antibodies are usually IgG-mediated but may be from an IgE isotype. These reactions can be prevented by using sufficiently washed red blood cells or by using blood from IgA-deficient donors (288).

Serum protein aggregates (nonimmune complex), such as human albumin, human γ globulin, and horse antihuman lymphocyte globulin, can cause anaphylaxis. These complexes likely activate complement, resulting in release of bioactive mediators. Cryoprecipitate and factor VIII concentrate have been

reported as causes of anaphylaxis. An IgE-mediated mechanism was demonstrated in one patient by leukocyte histamine release; positive skin test results to factor VIII, factor IX, and cryoprecipitate; and positive radioallergosorbent test (RAST) results to factor VIII. An attempt at pretreatment with corticosteroids and diphenhydramine and an attempt to desensitize did not prevent future reactions. The incidence of horse antilymphocyte globulin anaphylaxis is nearly 2%. Skin testing should precede use of such preparations to identify the presence of IgE antibodies (310–312).

Patients who are genetically deficient in haptoglobin and carry the anti-haptoglobin antibody may react against the haptoglobin protein in blood products, suggesting a need to identify these individuals by pretransfusion genotyping for haptoglobin (128).

Anaphylaxis from human seminal fluid by coital exposure rarely occurs with more than 30 cases reported since the initial report in 1958. It is IgE-mediated; the allergens are seminal-fluid proteins of varying molecular weight. Exogenous allergens may also be transferred in seminal fluid to a woman from a male partner's ingestion of food or drug to which the woman is sensitized. Skin testing can be done with the male partner's fresh whole human seminal plasma or its fractions. Conception is possible through artificial insemination with sperm devoid of seminal plasma proteins (washed spermatozoa). IT with seminal plasma fractions of the male partner has been successful in couples wishing to conceive. Also, treatment includes intravaginal graded challenge to dilutions of whole seminal fluid. Anaphylaxis can also be avoided by abstinence, regular use of condoms, as well as artificial insemination to achieve pregnancy. Auto-injectable epinephrine should be available (5,313,314).

EXERCISE-INDUCED ANAPHYLAXIS AND FOOD-DEPENDENT EXERCISE-INDUCED ANAPHYLAXIS

EIA may occur with any type of exercise, including running, cycling, and resistance, and may produce shock, loss of consciousness, and is potentially fatal. EIA has been described in high performance athletes and in individuals with occasional mild activity. EIA is generally reported following submaximal exercise of a relatively short duration. EIA may occur independently of food ingestion, or may require the ingestion of a food either before or less commonly after exercise, known as food-dependent EIA (FDEIA). The most important single cofactor is food, with other cofactors identified including exposure to warm or cold temperature, menstrual cycle, metal-containing dental amalgams,

and drug intake, especially NSAIDs. EIA occurs in all ages, both sexes, and is more common in atopic individuals with an estimated prevalence of 0.048%. Jogging is the most common activity; however, it has also been attributed to brisk walking, bicycling, racquet sports, skiing, and aerobics. Symptoms may include warmth, pruritus, erythema, urticaria, angioedema, nausea, vomiting, abdominal cramps, diarrhea, laryngeal edema, bronchospasm, respiratory distress, and vascular collapse. Fatalities are rare. Symptoms last 30 minutes to few hours. The reaction typically begins during or after exercise is completed and may occur only when exercise is performed shortly after a meal or a medication has been ingested, especially an NSAID or aspirin. EIA may rarely occur in an atopic individual exercising during high pollen levels. Unlike cholinergic urticaria, EIA is not from elevated body core temperature. EIA does not occur with each period of exercise, and the same amount of exercise on each occasion may not lead to anaphylaxis. Hence, exercise challenge testing does not consistently reproduce symptoms and is not necessarily a useful part of the evaluation. Dyspnea with a choking sensation occurs in 60% of patients and loss of consciousness occurs in 30% patients. Specific foods that have been linked to FDEIA include wheat, several vegetables, cereals, nuts, fish, cow's milk, beef, pork, chicken/turkey, snails, and mushrooms. These foods are tolerated without exercise, and exercising without eating these foods does not cause anaphylaxis. Eighty per cent of the patients have symptoms within 2 hours of eating, most often within 30 minutes from the onset of physical activity; however, a case occurred 5 hours after a wheat-containing meal (315–317).

The mechanism of action may involve an IgE mechanism with positive food skin-prick and positive food-specific IgE tests in most patients. As with EIA the pathophysiologic and immune mechanisms of FDEIA remain unclear; however ω-5-gliadin (Tri a 19) is the most common component related to wheat-dependent, EIA (230,315). The effectiveness of prophylactic treatment with H1 and H2 antagonists is inconsistent and may not prevent or reduce the severity or intensity of the episode. Patients with FDEIA should avoid exercise in the immediate postprandial period (e.g., 4 to 6 hours), when their particular trigger food or meal, or food with a NSAID/Aspirin was ingested. Each patient should recognize their unique exercise threshold as well as the early clinical manifestations necessitating prompt cessation of exercise; continued exertion can worsen the episode. FDEIA patients should carry two doses of auto-injectable epinephrine and exercise with a companion familiar with recognizing the signs and symptoms of FDEIA and be familiar with emergency treatment measures (5,315,316,318,319).

IDIOPATHIC ANAPHYLAXIS, ANAPHYLAXIS IN CLONAL MAST-CELL DISORDERS AND MAST-CELL ACTIVATING DISORDERS

IA was first described by Bacal and colleagues in 1978 with subsequent reporting in the 1990s from European countries including Spain, France, Ireland, Germany, and Brazil (320–322). IA is a diagnosis of exclusion of hitherto reviewed causes and mimickers of anaphylaxis. Patterson and colleagues (323) in 1995 estimated the number of IA cases in the United States to be between 20,592 and 47,024. In several reported patient series, 24% to 59% of anaphylaxis cases were classified as IA. IA has a higher prevalence in women compared to men, and IA patients are more likely to be atopic (324). IA occurs in both adult as well as pediatric population. The clinical manifestations of IA are the same as episodes of anaphylaxis resulting from known causes. Despite early use of epinephrine auto-injectors, patients may continue to experience life-threatening events, and fatalities may occur.

The pathophysiology of IA remains unclear despite numerous clinical and experimental studies. Markedly, Grammer and colleagues used flow cytometric analysis of lymphocytes markers to evaluate potential immunologic differences between normal control patients and IA patients during remission and acute episodes. Lymphocyte activation was demonstrated in IA patients compared with normal patients. The findings suggested that IA is an immunologic activation phenomenon consistent with the established clinical pattern of a steroid responsive disease (325).

The classification of IA is shown in Table 14.4. IA classification is based on frequency of episodes and clinical manifestations. Frequent (F) episodes are defined as having at least two episodes in the preceding two months or at least six episodes in the preceding year. The category is infrequent (I) IA, if the previous two criteria are not met. Generalized (G) IA-G is characterized by urticarial and/or angioedema in addition to systemic symptoms, such as cardiovascular, respiratory, and/or gastrointestinal. Patients are categorized asIA-angioedema (IA-A), characterized by significant upper-airway obstruction because of angioedema of the tongue, pharynx, or larynx in the absence of other signs of systemic anaphylaxis; these patients may also have urticaria. If the category of IA is unclear and cannot be classified as either IA-G or IA-A, it is classified as IA-questionable (IA-Q). IA-Q describes a patient with possible IA, who lacks documented objective findings and response to prednisone treatment.

IA-variant (IA-V) describes patients whose symptoms and clinical findings differ from classic IA. Undifferentiated somatoform IA (US-IA) is applied to patients who describe symptoms consistent with IA and lack an organic disease or documented objective findings, are nonresponsive to IA treatment regimens, and meet DSM criteria for an undifferentiated somatoform disorder. The patients with US-IA present significant diagnostic and management challenges associated with considerable health-care costs (326–328).

The treatment of IA is individualized based on the patient's particular IA category and presenting symptoms and physical findings. All IA patients receive education on recognition of and instruction on the management of an acute episode and are required to carry auto-injectable epinephrine (preferably two), prednisone 60 mg, and an H1 antihistamine (e.g., cetirizine). Acute management of IA begins with the first signs and symptoms of anaphylaxis. Initially, the patient should self-inject epinephrine 0.3 mL (1:1,000) intramuscularly in the upper lateral thigh and ingest prednisone 60 mg and a H1 antihistamine, such as cetirizine 10 mg. Other H1 antihistamines are acceptable. The epinephrine dose may need to be repeated in case of a poor response, particularly if the patient is on a β-blocker, ACE-Is, or both. The patient should seek emergency medical care depending on the circumstances, contact a physician for advice, call 911, or proceed to an emergency department where additional intensive therapy may be required (see Anaphylaxis Treatment and Prevention section subsequently).

IA is a corticosteroid-responsive condition, and patients with frequent episodes of IA (IA-AF, IA-GF) require daily H1 antihistamine and have their acute treatment/emergency plan at the ready. Patients with frequent episodes require prednisone therapy to induce control and remission. The dose is 40 to 60 mg once daily for 1 week or until the symptoms are controlled, along with a daily H1 antihistamine (e.g., hydroxyzine 25 to 50 mg three times a day or cetirizine 10 mg twice daily). Higher doses of prednisone may be required in some patients to control symptoms daily for 1 to 2 weeks, followed by a slow alternate-day taper by 5 mg every 1 to 2 weeks. Once prednisone is successfully tapered off, the antihistamines may be gradually tapered and/or discontinued. Patients who are not able to taper of prednisone are classified as corticosteroid-dependent IA (CSD-IA). If the prednisone dose required to control IA is at least 20 or 60 mg every other day, the IA is classified as malignant corticosteroid-dependent IA (MCSD-IA). In these patients, other drugs may be considered in attempting to taper off prednisone, including and not limited to H2 antihistamines, oral cromolyn, ketotifen, montelukast, and omalizumab. Ketotifen, a mast-cell stabilizer, not available in the United States, has allowed

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tapering and eventual discontinuation of prednisone in a series of five patients with severe IA or CSD-IA. Omalizumab has also been found to induce remission in IA patients recalcitrant to other therapies (326,327,329–333).

TABLE 14.4 CLASSIFICATION OF IDIOPATHIC ANAPHYLAXIS

DISEASE	SYMPTOMS
IA-generalized-infrequent (IA-G-I)	Urticaria or angioedema with bronchospasm, hypotension, syncope, or gastrointestinal symptoms with or without upper airway compromise with infrequent episodes (fewer than 6 episodes occurring per year)
IA-generalized-frequent (IA-G-F)	Clinical manifestations as for IA-G-I with at least 2 episodes during the preceding 2 months or at least 6 episodes in the preceding year
IA-angioedema-infrequent (IA-A-I)	Angioedema with upper airway compromise (laryngeal, pharyngeal, or tongue) without other systemic manifestations, urticaria may be present, infrequent episodes (fewer than 6 episodes preceding year
IA-angioedema-frequent (IA-A-F)	Clinical manifestations as for IA-A-I with at least 6 episodes in preceding year and at least 2 episodes in the preceding 2 months
IA-questionable (IA-Q)	Presumptive diagnosis of IA for which repeated attempts at documentation of objective findings are unsuccessful, response to appropriate doses of prednisone do not occur, and the diagnosis of IA becomes uncertain.
IA-variant (IA-V)	Symptoms and physical findings of IA vary from classic IA; IA-V may subsequently be classified as IA-Q or IA-excluded, IA-A or IA-G.
IA-undifferentiated somatoform (IA-US)	Symptoms mimic IA, no objective findings are discovered and there is no response to IA treatment regimens.

The prognosis of IA is generally favorable. In a retrospective study of 37 patients with IA ranging from 26 to 71 years, frequent episodes of IA defined as greater than five episodes per year occurred in 31% at presentation. At follow-up, 21 patients (60%) had resolution of IA and the frequency of anaphylaxis decreased in 9 patients, increased in 2 patients, and remained constant in 3 patients. Three patients still experienced frequent episodes, and two required chronic steroids. Patients with frequent IA treated only with antihistamines achieved remission or improvement at the same rate compared to chronic steroids (334). In studies from Northwestern University, the overwhelming majority of patients achieve remission (55,335,336). In a study by Alonso and colleagues assessing the risk of different subtypes of anaphylaxis, recurrence of anaphylaxis was higher for IA, foods, and exercise compared with other subtypes of anaphylaxis, such as from medications and hymenoptera stings (337).

The ratio of pediatric IA to adult IA cases is about 1:20. For this reason, the diagnosis of IA in children may be more delayed than the diagnosis in adults. Fortunately, the response to the above regimen for IA (with adjustment of doses for the pediatric population) appears equally successful and the prognosis equally favorable as in majority of adults (335).

Anaphylaxis is a frequent presentation of clonal mast-cell disorders, particularly in mastocytosis patients without skin lesions. The presence of cardiovascular symptoms, e.g., hypotension, occurring after a hymenoptera sting, or spontaneously in the absence of cutaneous manifestations such as urticaria is characteristic and differs from the presentation of anaphylaxis in the general population without mastocytosis. MCADs resemble mastocytosis and can cause anaphylaxis. Anaphylaxis can present across all subtypes of systemic mastocytosis (SM). MCADs and SM can be responsible for episodes previously thought to be from IA. The importance of establishing the fact that SM and MCADs can be the potential cause of IA is the fact that MCADs occasionally are controlled with tyrosine-kinase inhibitors (TKIs), and in the future a TKI(s) might be developed to control SM. Baseline elevations in serum tryptase, plasma histamine, 24-hour urinary histamine metabolites, or PGD_2 suggest these conditions. SM and MCADs can present in patients with lower levels of serum tryptase than the typical cutoff value of 20 ng/mL. A screening test performed to detect 816V KIT mutation can establish mastocytosis in most cases, but the most definitive way to make a diagnosis of mastocytosis is to obtain a bone marrow

biopsy. Thus, any patient with repeated episodes of anaphylaxis with unknown cause should have a baseline (asymptomatic) serum tryptase assay because an elevated level suggests these diagnoses. In such patients, a bone marrow biopsy evaluated by appropriate immunohistochemical staining should be considered. To assist in confirming a diagnosis of anaphylaxis in these patient types, the patients should be given a letter or physician order to obtain during an episode at the emergency department, measurement of serum tryptase, plasma histamine, 24-hour urinary histamine metabolites, and PGD_2 (338–345) (Table 14.5)..

ANAPHYLAXIS MANAGEMENT AND PREVENTION

The treatment of anaphylaxis should follow established principles for emergency resuscitation. Anaphylaxis has a highly variable presentation, and treatment must be individualized for a patient's particular underlying medical conditions, concurrent medications, symptoms, and their severity. Determine whether the patient has risk factors for severe and potentially fatal anaphylaxis, such as delayed administration of epinephrine, asthma, a history of biphasic reactions, or cardiovascular disease, and consider these in the management and/or disposition of all patients with anaphylaxis. Management recommendations are subject to physician's discretion and variations in sequence and performance rely on the physician's judgment. Prompt recognition followed by rapid therapy is of utmost importance including a treatment log to accurately record progress. Medical facilities should be stocked with anaphylaxis supplies with expiry dates recorded: injectable epinephrine, intravenous fluids, needles, oxygen cannula and mask, oral airways device, stethoscope, and a sphygmomanometer as minimal essentials. The approach outlined in Table 14.6 is required to counteract the effects of mediator release, support vital functions, and prevent further release of mediators. In healthcare settings where allergen skin tests or allergen challenge/provocation tests are performed or allergen-specific IT, anti-IgE antibody injections, or vaccine injections are given, it is important to develop and rehearse anaphylaxis management plans (customized written protocols) with trained staff and ensure availability of essential medications, as well as essential supplies and equipment. The duration of direct observation and monitoring after an anaphylaxis episode should be individualized, providing longer periods of observation for those patients with a history of risk factors for severe anaphylaxis (e.g., asthma, previous biphasic reactions, or protracted anaphylaxis) for at least 4 to 8 hours. Patients at risk for anaphylaxis must be provided with an action plan instructing them how to manage an episode of anaphylaxis, including self-administration of epinephrine (5,24,346).

At the first sign of anaphylaxis, the patient should be treated with epinephrine. Next, determine whether the patient is dyspneic or hypotensive. Airway patency must be assessed, and if the patient has suffered cardiopulmonary arrest, basic cardiopulmonary resuscitation must be instituted. The use of cricothyrotomy should be reserved for life-and-death situations where obstruction above the larynx prevents adequate ventilation. If shock is present or impending, the patient should not attempt to sit or stand, and should be placed in a supine position (pregnant patients on their left side) and the lower extremities should be elevated and intravenous (IV) fluids administered (1 to 2 L of 0.9% normal saline infused rapidly, e.g., 5 to 10 mL/kg within the first 5 minutes for an adult and up to 30 mL/kg in the first hour for children, with large bore (14- to 16-gauge adult) IV catheters. Epinephrine is the most important single agent in the treatment of anaphylaxis, and its delay or failure to be administered is more problematic than its administration. There are no absolute contraindications to the use of epinephrine, including patients with heart disease who experience anaphylaxis. However, several anaphylaxis fatalities have been attributed to injudicious IV epinephrine administration. Administer aqueous epinephrine 1:1,000 dilution, 0.3 to 0.5 mL (0.01 mg/kg in children to a maximum 0.3 mg) intramuscularly (IM) in the anterolateral thigh every 5 to 10 minutes as necessary. Alternatively, an epinephrine auto-injector may be administered through clothing into the anterolateral thigh. IV epinephrine should be used only in patients with severe hypotension-cardiovascular collapse or terminal or grave clinical status not responding to IM epinephrine and aggressive IV fluid replacement, including colloid-containing solutions if necessary. IV administration of epinephrine will rarely be necessary in the outpatient setting and should be administered in a monitored setting with a programmable infusion pump to titrate appropriately. However, if there is no response to multiple injections of IM epinephrine and IV fluid replacement in combination with a delay in EMS response, prolonged transport, or cardiopulmonary arrest and resuscitation, then IV epinephrine may be required. There is no established dosage or regimen for IV epinephrine in anaphylaxis. However, a prospective study demonstrated the efficacy of 1:100,000 solution of epinephrine IV by infusion pump at the initial rate of 2 to 10 µg/minutes titrated up or down depending on the clinical response or epinephrine side effects. Despite the lack of controlled studies to evaluate the efficacy of alternative vasopressors in the setting of refractory hypotension dopamine, norepinephrine and vasopressin have been suggested with the requirement of a second infusion pump, preferably in a hospital setting with continual electronic monitoring of heart rate and rhythm, blood pressure, and oxygen saturation (5,148,347–350).

TABLE 14.5 DIFFERENTIAL DIAGNOSIS OF IDIOPATHIC ANAPHYLAXIS

Hereditary and acquired angioedema, systemic mastocytosis, mast-cell activating syndrome, vasovagal reaction, carcinoid, pheochromocytoma, vasointestinal polypeptide tumors, medullary carcinoma of the thyroid, red man syndrome, capillary leak syndrome

Hidden allergens (e.g., food, drug, latex, pollens, supplements and other known causes of anaphylaxis)

Exercise with or without preceding food/drug

Restaurant syndromes: scrombroidosis, monosodium glutamate, ingestion of histamine-rich food

Munchausen anaphylaxis/stridor, prevarication and malicious anaphylaxis, somatoform idiopathic anaphylaxis, panic attacks, vocal-cord dysfunction

TABLE 14.6 MANAGEMENT OF ANAPHYLAXIS

Immediate:

1. Aqueous epinephrine 1:1,000 dilution, 0.3–0.5 mL (0.01 mg/kg in children; maximum 0.3 mg) IM in thigh. May repeat every 5–10 minutes if necessary. For systolic blood pressure <90 mm Hg adult <50 mm Hg children, elevate lower extremities (place pregnant patient on left side). IV fluids 1–2 L of 0.9% normal saline 5–10 mL/kg within first 5 minutes for an adult and up to 30 mL/kg in the first hour for children with large bore (14- to 16-gauge adults) IV catheters. IV epinephrine if severe hypotension-cardiovascular collapse or terminal-grave clinical status not responding to IM epinephrine and aggressive IV fluid replacement (if IV access is not available obtain IO access for fluid replacement and epinephrine administration). IV epinephrine dosing: 1:100,000 solution by IV pump at initial rate of 2–10 µg/min titrated up or down depending on the clinical response or epinephrine side effects. Consider alternative vasopressors in the setting of refractory hypotension; e.g., dopamine, norepinephrine, or vasopressin using a second infusion pump with continual electronic monitoring of heart rate and rhythm, blood pressure and oxygen saturation.

2. Oxygen administration for all patients experiencing anaphylaxis, especially for patients exhibiting respiratory or cardiovascular symptoms or with decreased

oxygen saturation. Prepare for airway management, including intubation if necessary. β-Adrenergic agonists may be used to treat bronchospasm not reversed by epinephrine. A β-agonist, such as albuterol, can be administered by a metered-dose inhaler (two to six inhalations) or by nebulizer (2.5–5 mg in 3 mL of saline and repeated as necessary).

3. Patients with anaphylaxis who are unresponsive to traditional resuscitative efforts should be considered candidates for extracorporeal membrane oxygenation, preferably before irreversible ischemic acidosis develops.

4. Patients taking β-adrenergic antagonists:

   a. Glucagon 1–5 mg (children 20–30 µg/kg, 1 mg maximum) IV slowly, then titrate at 5–15 µg/min infusion, emesis precaution.

   b. Atropine if bradycardia; 0.3–0.5 mg IM or IV every 10 minutes, to a maximum of 2 mg.

5. H1 and H2 antihistamines and corticosteroids (no published guideline consensus, considered second line or adjunctive therapy (antihistamine relief of urticarial itching):

   a. Diphenhydramine, IV slowly: 25–50 mg for adults; 1 mg/kg up to 50 mg maximum for children. Ranitidine: 50 mg for adults, 12.5–50 mg children (1 mg/kg) IV over 5–10 minutes.

   b. Methylprednisolone 1–2 mg/kg/dose up to 125 mg or an equivalent alternative corticosteroid.

6. The duration of observation and monitoring is individualized and based on the severity and duration of the anaphylactic event, response to treatment, pattern of previous anaphylaxis, medical comorbidities, patient reliability, and access to medical care. Moderate to severe anaphylaxis should be observed for 4–8 hours. Mild anaphylactic symptoms that occur in a medical setting and that rapidly resolve with treatment usually will require a shorter observation. A longer observation, including possible hospital admission, should be considered when risk factors for more severe anaphylaxis are present: history of severe asthma, allergens have been ingested, more than one dose of epinephrine is required, pharyngeal edema is present, and severe or prolonged symptoms are noted (e.g., prolonged wheezing or hypotension).

   At discharge from medical care, patients are to be provided with a prescription for two auto-injectable epinephrine devices and instructed on usage. Initiate an anaphylaxis action plan, with a permanent anaphylaxis care plan developed by a referral to an allergist who can obtain a detailed history, coordinate additional outpatient testing, and provide additional allergen-avoidance counseling and a patient specific action plan. A peer-reviewed standardized anaphylaxis plan is

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IM, intramuscular; IV, intravenous; IO, intraosseous; PO oral.

Oxygen should be administered to any patient exhibiting respiratory or cardiovascular symptoms or patients with decreased oxygen saturation and consider for all patients experiencing anaphylaxis regardless of their respiratory status. Prepare for airway management, including intubation if necessary, if there is any suggestion of airway edema (e.g., hoarseness or stridor) or associated respiratory compromise. Asphyxia can occur because of upper-airway swelling or bronchospasm. B-adrenergic agonists may be used to treat bronchospasm not reversed by epinephrine. A β-agonist, such as albuterol, can be administered by a metered-dose inhaler (two to six inhalations) or nebulizer (2.5 to 5 mg in 3 mL of saline and repeated as necessary). Patients with anaphylaxis who are unresponsive to traditional resuscitative efforts should be considered candidates for extracorporeal membrane oxygenation, preferably before irreversible ischemic acidosis develops (346).

The use of β-blockers, both oral and ophthalmic, has been linked to unusually severe refractory anaphylaxis with paradoxical bradycardia, profound hypotension, and severe bronchospasm related in part to a blunted response to epinephrine administered to treat anaphylaxis. Epinephrine administered to a patient taking a β-blocker can produce unopposed α-adrenergic and reflex vagotonic effects, possibly leading to hypertension and the risk of cerebral hemorrhage. In patients receiving β-blockers, increased propensity not only for bronchospasm but also for decreased cardiac contractility with perpetuation of hypotension and bradycardia is possible. If epinephrine is ineffective in treating anaphylaxis in patients taking β-blockers, glucagon administration may be necessary. Glucagon can reverse refractory bronchospasm and hypotension during anaphylaxis in patients on β-blockers by activating adenyl cyclase directly bypassing the β-adrenergic receptor. The recommended dose for glucagon is 1 to 5 mg (children 20 to 30 µg/kg 1 mg maximum). Airway protection is required for possible glucagon-induced emesis and aspiration. If IV access is not readily available, obtain intraosseous (IO) access for both fluid replacement and epinephrine administration. Epinephrine can be infused by IO at a rate of 1 µg/minutes and titrated to a maximum of 10.0 µg/minutes for adults and adolescents. A starting dose of 0.1 µg/kg per minute is recommended for

children. There is no consensus among published anaphylaxis guidelines regarding the use of H1 and H2 antihistamines, or glucocorticoids in the treatment of anaphylaxis. These agents are considered second-line treatment drugs in the management of anaphylaxis. H1 and H2 antihistamines do not prevent or treat upper-airway obstruction or hypotension. H2 antihistamines (e.g., cimetidine) can increase hypotension. H1 antihistamines relive symptoms (e.g., urticarial itching). Though sedating, diphenhydramine is available for IV administration. The dose of diphenhydramine is 25 to 50 mg in adults and 1 mg/kg to a maximum of 50 mg in children administered IV over 10 to 15 minutes. The preferred oral H1 antihistamine is nonsedating cetirizine with an onset of action equal to or more rapid than that of oral diphenhydramine. The H2 antihistamine ranitidine may be administered parentally; dose is 1 mg/kg for adults and 12.5 to 50 mg in children IM or slow IV infusion. Corticosteroids have no role in the acute management of anaphylaxis, and patients who have complete resolution of symptoms after treatment with epinephrine do not need to be prescribed antihistamines or corticosteroids thereafter. The evidence that corticosteroids produce a decrease of biphasic or prolonged anaphylaxis is not supported by strong evidence, with their use and doses being extrapolated from those used to treat acute asthma. When administered, the oral and IV dose recommended is 1 to 2 mg/kg/dose up to 125 mg of methylprednisolone or an equivalent formulation. Do not routinely administer antihistamines or corticosteroids instead of epinephrine. There is no substitute for epinephrine in the treatment of anaphylaxis. Administration of H1 and/or H2 antihistamines and corticosteroids should be considered adjunctive therapy (5,346).

The duration of direct observation and monitoring after an episode of anaphylaxis is individualized based on the severity and duration of the anaphylactic event, response to treatment, pattern of previous anaphylactic reactions, medical comorbidities, patient reliability, and access to medical care. Patients with moderate severe anaphylaxis should be observed for a minimum of 4 to 8 hours. Mild anaphylactic symptoms that occur in a medical setting and that rapidly resolve with treatment usually will require a shorter observation. A longer observation, including possible hospital admission, should be considered when risk factors for more severe anaphylaxis are present: history of severe asthma, allergens have been ingested, more than one dose of epinephrine is required, pharyngeal edema is present, and severe or prolonged symptoms are noted (e.g., prolonged wheezing or hypotension).

At discharge from medical care, patients are to be provided with a prescription for auto-injectable epinephrine and instructed on when and how to

use it. Encourage the patients to immediately fill this prescription, 23% of patients may experience a biphasic reaction, usually within 10 hours after resolution of the initial event. Two epinephrine auto-injections should be provided because up to 30% of patients who develop anaphylaxis will require more than one dose of epinephrine. In the United States, two doses (0.15 and 0.30 mg) are available. The adult dose is 0.30 mg. In children, the dose is 0.01 mg/kg to a maximum of 0.30 mg). Giving a dose that is slightly above the ideal dose is better than giving a dose that is below the recommended dose (5,346).

Campbell and colleagues concluded that 8% of patients required an additional dose of epinephrine for the initial management of an anaphylactic reaction supporting the current guidelines recommending that patients with anaphylaxis should carry two epinephrine auto-injectors. Patients with a history of anaphylaxis, who presented with diaphoresis or flushing or dyspnea, were more likely to require multiple doses of epinephrine. Patients who required more than one dose of epinephrine were more likely to be admitted to the hospital, resulting in increased use of health-care resources (351).

The initial anaphylaxis action plan should begin at the point of care, with a permanent anaphylaxis care developed by an allergist working with the patient, primary-care physician, family, associated members of the interdisciplinary clinical team, and the school, when appropriate. The allergist can obtain a detailed history (ingested foods/drugs within 6 hours of event, activity and time of day, season, heat or cold exposure, exact symptoms and observed physical findings, menses timing in women, medical care and administered treatments, recurrence history, and laboratory/procedure review) and coordinate additional outpatient testing, provide additional allergen-avoidance counseling (label reading, informing food handlers, updating drug/food/insect/exercise/idiopathic allergy in the electronic medical record), specialty treatment such as venom IT, medication desensitization/graded challenges/induction of tolerance/alternative medication recommendations/pretreatment regimens, when to advise exercise with a companion, develop a detailed emergency action plan for future reactions, and provide the patient with access to medical identification jewelry or wallet card. A peer-reviewed standardized anaphylaxis plan is recommended that has been developed by lay support groups in conjunction with national allergy organizations (e.g., www.foodallergy.org/document.doc?id=234, www.allergyasthmanetwork.org/outreach/publications/special-publications/anaphylaxis-guide-for-all/). The action plan should indicate in simple, clearly stated language and/or figures the signs and symptoms of anaphylaxis, the patients' known triggers, and the first and only mandatory drug

to be administered (epinephrine), regardless of how mild the symptoms are. Further instructions to be listed in order are to call 911 and, if appropriate, notify the patient's family. Whether to list on the action plan the administration of any medications other than epinephrine (e.g., nonsedating oral antihistamine and/or prednisone) should be left to the allergist who can decide on a case-by-case basis (5,346).

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Allergy to Stinging Insects

THEODORE M. FREEMAN

INTRODUCTION

As with nearly every diagnosis in medicine, the history is paramount when dealing with insect allergy. While the history may seem straightforward, it often suffers from considerable uncertainty with insect stings. The diagnostic criteria for anaphylaxis are clear, but insect stings often provoke considerable anxiety. Is a sense of impending doom a symptom of anaphylaxis or of anxiety? Is the shortness of breath because of bronchospasm or hyperventilation? Did the patient fall asleep because they took an antihistamine or because they were hypotensive? There is seldom clarifying information available like emergency room records or a witness who was with the patient, and one is left to use one's clinical acumen to make a decision. Generally, the author takes a very conservative approach and any sign or symptom that might lead to a diagnosis is considered just that, i.e., signs or symptoms of anaphylaxis.

The identification of the insect involved is often just as uncertain. The patient is usually quite certain of their identification, but in fact often completely misidentify the hymenoptera involved (1). Consideration of the circumstances involved in the sting event can sometimes suggest a particular species of flying hymenoptera (see further), but there remains considerable uncertainty in most cases leading to the recommendation of testing for all flying hymenoptera in most cases (2). Fire ants are an exception to this rule. As they are much smaller than other hymenoptera, the workers do not have wings and usually a distinctive sterile pustule develops at the site of the sting within 24 hours; the clinician can usually be fairly certain when the culprit was a fire ant.

Excellent studies support the definitive prophylactic therapy for insect sting hypersensitivity, but while research is active, it is hampered by small numbers of patients leading to more uncertainty concerning many items for example how diagnostic tests are interpreted, how long venom immunotherapy (VIT) should be used, and what cofactors are of importance in these patients. This chapter reviews what the state of practice is at this time.

THE INSECTS

There are only a few insects, all belonging to the order Hymenoptera, that are of clinical importance in North America. These include the European honeybee (HB) *Apis mellifera*, the Africanized honeybee (AHB) *Apis mellifera scutellata*, the bumblebee (BB) various species of *Bombus*, the wasp (W) various species of *Polistes*, the yellow jacket (YJ) *Vespula* species, the baldfaced hornet and yellow hornet (BFH and YH) *Dolichovespula* species, the European hornet (H) *Vespa crabro*, and the fire ants (FA) (*Solenopsis invicta* and *Solenopsis richteri*). These later species are often called "imported" as they are native to South America and not North America. The native fire-ant species may sting but much less frequently than the imported species. Some of these Hymenoptera have more restricted geographic locations. AHBs are found mostly in the southern United States (Fig. 15.1), and European hornets mostly in the eastern one-third of the United States. The fire ants are mostly found in the southeast gulf coast but have spread as far north as Tennessee and west as far as Southern California (Fig. 15.2).

Some of these species are very aggressive, such as the YJ and the AHB. Nearly all are aggressive near their hives or nests. A few sting only when severely provoked, e.g., HB and BB.

HB and BB have been domesticated and are useful to improve agricultural pollination. HB are usually found in manmade hives, whereas BB have been used in greenhouses in Europe (3). In nearly all cases, they need to be trapped between clothing and skin or between skin and the ground in order to sting. The typical scenario can be walking barefoot in a flower meadow and stepping on one. Because HBs have a barbed stinger that gets trapped in skin after stinging, they eviscerate their venom sac and stinging the apparatus when flying away after stinging. This gets HB killed but helps in identification. HB were interbred with African species to make them hardier resulting in the AHB. They are hardier and much more aggressive results in stinging and any perceived threat, often swarming and following intruders for miles.
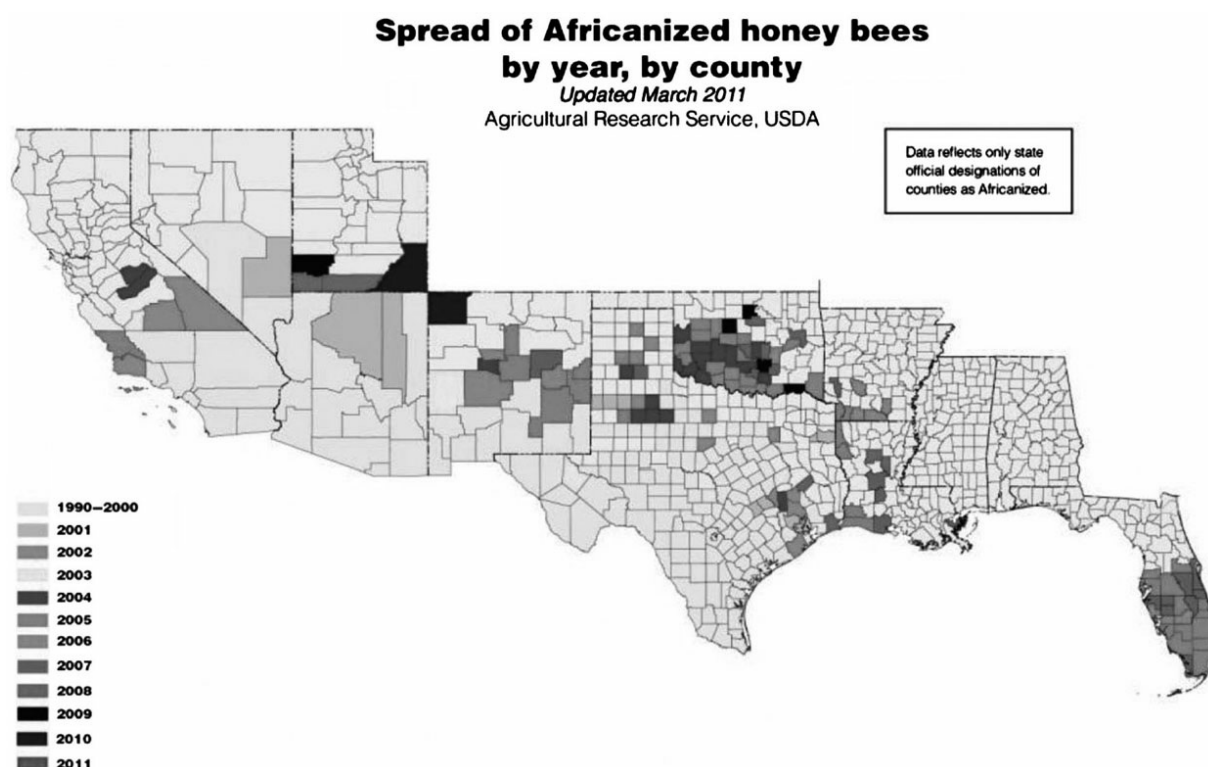
■ FIGURE 15.1 Spread of Africanized honey bees by year, by county.

YJs build multileveled paper nests that are completely enclosed with paper wall. In addition, they build nests within preexisting holes like old burrows or hollows in trees. They are very aggressive scavengers and are often found around any potential food source. A typical scenario for a sting with these insects can be at a picnic spot where food is being served or near an open garbage can. Cases of oropharyngeal stings have occurred when patients have drunk from an open beverage can in which a YJ had already crawled into. YJ occasionally also leaves a stinger after stinging; presence of a stinger after a sting is not definitive for an HB.

BFHs and YHs build nests like YJs, but their preferred location is hanging from a branch of a tree or shrub. The typical sting event here is accidently getting to close to a nest while working, walking, or playing (e.g., golfing) near woods and shrubs.

Ws build open-faced single-level nests that hang by a pedicel from structures built by us such as the eaves of our porches. A typical W sting often occurs around our homes.

Rather than build a paper nest as most of the other hymenoptera, ants excavate a nest out of the ground. FAs are no exception; if excavating in moist clayey soil, a mound may be a foot high and several feet in circumference, but in dry sandy soil the mound may be completely flat. As fire ants do not denude the

area around their nests and like to build in disturbed soil, such as agricultural fields and at the edge of sidewalks and roads, people living in endemic areas are often exposed to them. If their mounds are disturbed hundreds to thousands of ants will respond and a typical event for FAs is to accidently disturb a mound and then find multiple ants biting (holding on with their jaws) and stinging the patient. Each ant can sting multiple times resulting in an arc of stings that the next day develop into an arc of sterile pustules.

REACTIONS

The usual reaction after an insect sting involves a small area (1 to 2 cm) of swelling with a central puncta and surrounding erythema. This usually resolves in several hours. As mentioned before for FAs, a sterile pustule develops about 24 hours later. Opening these sterile pustules is much more likely to lead to infection and consequently it is recommended not to open them. If done accidently, FA stings should be kept clean with soap and water.
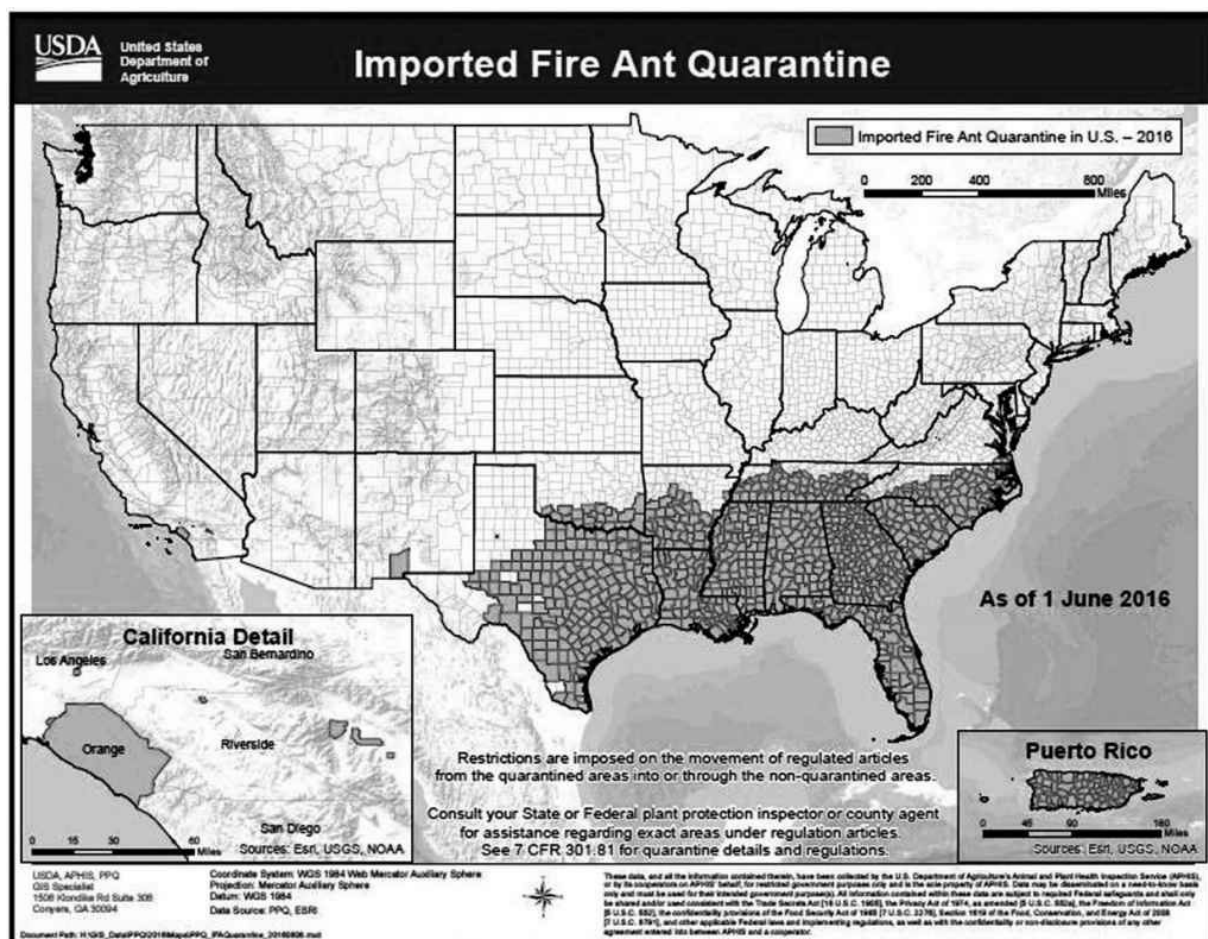
■ **FIGURE 15.2** Imported fire ant quarantine.

Sometimes after a hymenoptera sting, the swelling at the site of the sting

continues to progress for 2 to 3 days and may reach 10 cm or more before beginning to recede and may take a week or more to resolve completely. These are termed large local reactions (LLR). LLR are not signs of infection and do not require antibiotics.

Systemic reactions can occur that do not meet the criteria for anaphylaxis. This is the case with a generalized cutaneous reaction, e.g., pruritus, urticaria, or angioedema not occurring at the site of the sting.

Of most concern is anaphylaxis, which is diagnosed when signs or symptoms involving at least two of the following four organ systems are present, or when hypotension is documented after a sting. Organ systems involved may include cutaneous (flushing, hives, angioedema, pruritus), pulmonary (shortness of breath, wheezing, chest tightness, cough), gastro-intestinal (GI)/genito-urinary (GU) (abdominal or pelvic cramping, nausea, vomiting, diarrhea), or cardiovascular (tachycardia, dysrhythmia, hypotension, syncope). Diagnostic criteria for anaphylaxis also include an isolated drop in blood pressure (30 mm Hg systolic in an adult) after a known exposure to an agent which has previously caused anaphylaxis. Onset of anaphylaxis may occur very quickly (minutes) after an insect sting in a sensitized patient. Progression from onset of symptoms to severe life-threatening symptoms may occur within minutes as well. Biphasic anaphylactic reactions can occur with a recurrence of symptoms several hours after the initial symptoms have cleared. Estimates range from 30 to 50 deaths a year as a result of anaphylaxis after insect stings in the United States (2,4). At autopsy, patients dying from insect stings because of anaphylaxis are usually found to have severe edema and mucous production in the airway causing obstruction, but occasionally nothing specific is found suggesting a dysrhythmia with hypotension as the cause of death (5,6). This latter absence has led to the suggestion that additional unobserved deaths attributed to cardiovascular causes might actually be the result of insect stings, thus leading to the proposal that more deaths may occur because of hymenoptera stings than those clearly documented.

Massive envenomation can potentially lead to a cardiovascular death from the direct action of vasoactive proteins contained in the venom. Studies carried out in rodents with HB venom suggest a lethal dose 50 (a dose projected to cause at least 50% of subjects to die) of 41.6 mg/kg (7). Extrapolating to a 50 kg human, and recognizing that an average HB sting delivers about 50 µg of venom protein, means it would require thousands of stings to be lethal. It has been proposed that 9 to 19 honey bee stings/kg (of patient weight) in the setting of severe initial

reaction may be an indication for plasmapheresis or exchange transfusion to prevent additional toxic symptoms (8). Many cases of unusual reactions after insect stings have been reported. These include neuropathies, nephropathies, and hematologic reactions, such as serum sickness like reactions (9,10). The mechanism for these reactions in the setting of massive envenomation could be immune complex mediated, but the case reports often deal with much smaller doses so the mechanisms involved remain speculative.

■ TESTING FOR SPECIFIC IgE

In order for anaphylaxis to occur, a patient has to have had preformed specific IgE to at least one venom component (Table 15.1). Therefore, if one is considering treatment with immunotherapy, specific IgE must be shown. Demonstration of specific IgE has traditionally been accomplished by the same methods used in testing for aeroallergens or environmental allergens. These are *in vivo* skin testing or *in vitro* tests utilizing techniques like immunofluorescence, or basophil activation. Hymenoptera venoms, except for FA which only has whole body extract (WBE) commercially available, are standardized for protein content and the presence of enzyme activity (phospholipase or hyaluronidase). Despite this, neither technique is considered a "gold standard" as specific IgE can be demonstrated by the other technique when the first was negative in up to 20% of cases (11). In fact, despite negative results to both methods occasional patients can still suffer anaphylaxis after a sting (11), suggesting we do not yet have perfectly sensitive tests (see subsequently).

Several possible causes for a lack of specific IgE in these patients have been proposed including that the patient tested by skin testing after a recent sting may be in a refractory period and that the venom used may have lost important antigens during their extraction and preparation. The former would affect only *in vivo* testing while the latter would affect both *in vivo* and *in vitro* testing. Another possible cause of negative tests for specific IgE is mast cell activation disease (MCAD) (12). If testing is truly negative in a patient with a convincing history of anaphylaxis after a sting, then serum tryptase should be ordered. If this is elevated then further evaluation for MCAD is indicated. Skin testing is considered the technique of choice as it more closely models the pathophysiology of anaphylaxis, but either skin testing or *in vitro* techniques is acceptable for demonstrating specific IgE. Generally, skin testing is carried out with progressive concentrations of antigen to ensure the presence of antibody and minimize the risk of a reaction to the test. Prick testing with 1 to100 µg/mL of the venom preparations (full-strength WBE for FA) is done first then

intradermal testing is done with three to four 1:10 dilutions up to 1 µg/mL (10 µg/mL if small irritant proteins have been dialyzed out) (13) or 1:100 of full-strength WBE (usually a 1:10 weight/volume (wt/vol)) for FA (2). Testing is stopped when a positive response is found. Definitive criteria for skin test positivity remain a point of discussion. Initial research protocols and package inserts suggest 5 to 10 mm of induration with 11 to 20 mm of erythema are required to call a test positive, but most clinicians appear to be satisfied with 3 to 5 mm of induration greater than the negative control with surrounding erythema (2). Anyone unable to generate a positive response to a positive control must have an *in vitro* technique employed.

TABLE 15.1 HYMENOPTERA VENOM COMPONENTS

Phospholipase A2	Api m 1, Bom t 1
Phospholipase A1	Ves v 1, Dol m 1, Pol a 1, Vesp c 1, Sol i 1
Hyaluronidase	Api m 2, Ves v 2, Dol m 2, Pol a 2
Antigen 5	Ves v 5, Dol m 5, Pola a 5, Vesp c 5, Sol i 3
Dipeptidyl peptidase IV	Ves v 3, Api m 5
Vitellogenin	Api m 12, Ves v 6
Acid phosphatase	Api m 3
Melittin	Api m 4
Protease inhibitor	Api m 6
CUB serine protease	Api m 7
Carboxylesterase	Api m 8

Serine carboxypeptidase	Api m 9
Icarapin	Api m 10
MRJP 8 and 9	Api m 11

Api m, *Apis mellifera;* Bom t, *Bombus terrestris;* Dol m, *Dolichovespula maculate;* MRJP, major royal jelly proteins; Pol a, *Polistes annularis;* Sol i, *Solenopsis invicta;* Ves v, *Vespula vulgaris;* Vesp c, *Vespa crabro.*

Modified from Danneels EL, Vaerenbergh MV, de Graaf DC. Hymenoptera venoms: toxicity, components, stability and standardization. In: Freeman TM, Tracy JM, eds. *Stinging Insect Allergy: A Clinician's Guide.* Switzerland: Springer International Publishing; 2017:48–50.

As it is often difficult to determine which species of hymenoptera actually caused the reaction (see earlier), testing is generally carried out with all the flying hymenoptera venoms. This frequently results in the patient having a positive response to more than one venom. Theoretically, this could be because of cross reactivity between the venoms (Table 15.1), or it could be because of a patient having more than one sensitivity, or it could be because of cross reacting carbohydrate side chains on the venom proteins. As selection among these options requires the use of techniques not routinely available to most clinicians, the general recommendation has been to consider all positives as true positives for making therapeutic judgments. The ability to test for components of venom or for the recombinant venom proteins, which do not have carbohydrate side chains, may allow refinement of this recommendation once they are commercially available in the future (14–17).

Component testing has been proposed to possibly improve the accuracy of testing, but studies so far have not shown it to improve the sensitivity of testing compared to whole venom (18–23). However, as mentioned before, one reason that venom testing may not be positive in all patients that have had a reaction to hymenoptera may be that some components of the total venom may have been lost during its extraction and preparation. As increasing the number of components tested increases the sensitivity of testing (21,24), if current venom preparations are shown to be deficient in certain antigens in the venom, then artificially producing those components and adding them to the current venom preparations used for testing may actually improve the sensitivity of current venom tests.

Basophil histamine release has been examined in patients with venom hypersensitivity. It may show equivalence to intradermal testing for detecting specific IgE (25), but is technically challenging and not commercially available at this time. It has also been used to determine if VIT is effective (26–30) and is clearly a safer method than the only other method for assessing effectiveness, which is sting challenges. Consequently, it may be a useful addition to our testing armamentarium in the future, when it becomes commercially available.

■ THERAPEUTIC APPROACH

As the usual reaction is self-limited and requires no treatment, usually cold packs, nonsteroidal anti-inflammatories, and antihistamines may minimize symptoms.

For LLR, the same modalities may be employed and of course may be continued until the symptoms resolve. Occasionally, oral steroids are used for more severe symptoms or ones associated with major morbidity such as reduced vision because of eyelid swelling or inability to walk because of foot swelling. Antibiotics are not indicated to treat LLRs.

Therapy for cutaneous systemic reactions, i.e., generalized hives and/or angioedema, is antihistamines. If anaphylaxis is diagnosed, then intramuscular epinephrine is the therapy. Systemic steroids do not affect the acute response and have not been shown to prevent a biphasic response and are not indicated.

H_1 antihistamines can help with cutaneous symptoms and β adrenergics can be useful for pulmonary symptoms. In cases of known prior anaphylaxis to insect stings, one may consider epinephrine use as soon as any symptoms develop even if they are just cutaneous.

The risk posed by future stings is a function of the results of prior stings (Table 15.2). Minimizing that risk involves avoiding stings, being prepared if stings occur, and prophylaxis to lower the risk of future reactions.

Avoiding future insect stings involves situational awareness. These patients should pay attention to their environment. Wasp nests should be removed from around the patient's home by someone, who is not sensitive to wasps, routinely. Patients who are hymenoptera-sensitive should avoid being around open food. Garbage areas, picnics, and outdoor gatherings where food is present are all possible draws for flying hymenoptera. In particular, such patients should never drink from open beverage cans where what is inside the can is not visible. Hymenoptera-sensitive patients should never walk around outdoors barefoot, and

in fire ant endemic areas should wear shoes and socks. Before sitting on the ground one should check for FA mounds or trails as well as meandering HBs and BBs. Gardeners in FA endemic areas should wear work gloves as well.

Anyone who is at risk for recurrent anaphylaxis should carry epinephrine auto-injectors. Assessment of the risk involves a consideration of many factors (Table 15.3). These include the severity of the prior reaction (see subsequently), the likelihood of exposure (outdoor work or avocation), medical conditions that increase the risk (see subsequently), and the concern the patient has for a potential event. If a patient is significantly concerned they should be prescribed an auto-injector even if the provider's assessment is that the patient is at low risk. Besides reviewing the use of the auto-injector prescribed, providers should instruct that patients who use an auto-injector should then proceed to an emergency-care facility, because the effect of the epinephrine is short (30 to 45 minutes) and anaphylaxis may persist for hours. Anyone issued an auto-injector should also be advised to obtain and wear medical alert jewelry, so that if a patient is found unconscious outdoors, a diagnosis of hymenoptera sting might be considered and treated.

Immunotherapy is very effective form of prophylaxis for future stings. The risk of anaphylaxis after a prior systemic reaction to a hymenoptera sting is in the 50% to 75% range. The more severe the reaction the more likely a systemic reaction will occur after a future sting (Table 15.2). Immunotherapy reduces that risk down to 2% to 3% for future stings (31,32). The next section will focus on the technical aspects of immunotherapy.

■ IMMUNOTHERAPY

The mechanism of action for immunotherapy has not been fully defined. Just as with immunotherapy for aeroallergens, we see a rise then fall of specific IgE (33). Specific IgG antibodies develop and can be passively transferred to block symptoms from a sting challenge (34), and higher levels of blocking IgG seem to correlate with protection (35), but these take months to develop. Studies of rush VIT show protection before blocking antibodies develop. One study in rush VIT patients show a decrease in IL-4 and IL-5 and increase gamma-interferon production (36). While another in both rush and conventional VIT showed a switch from a TH2 to a TH1 response (37). These studies are supportive of our understanding of the mechanism of action of immunotherapy but are not definitive.

Selection of patients who should be offered immunotherapy requires two

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criteria. First, the patient has to have suffered anaphylaxis, and, second, they have to have specific IgE to hymenoptera. The latter criteria is absolute. The former is a topic for discussion as there are people who may benefit from immunotherapy who have not suffered anaphylaxis (Table 15.4). Patients with cutaneous reactions may express only considerable anxiety about future stings and may be offered immunotherapy if they have specific IgE. Data show that both the size and duration of LLRs may be reduced by immunotherapy in patients with specific IgE (38,39). Consequently, patients who experience these reactions frequently may consider VIT. MCAD patients are known to be a very high-risk population for severe reactions after insect stings (40). As these patients are known to have severe initial reactions to hymenoptera stings and immunotherapy appears to be safe (41), one might discuss the possibility of checking for specific IgE and offering immunotherapy in patients with MCAD if there is significant risk of being stung in the future.

TABLE 15.2 RISKS OF FUTURE STING REACTIONS (Rx) BASED ON SEVERITY OF PREVIOUS REACTIONS

	CHANCE OF FUTURE SYSTEMIC Rx	
PREVIOUS STING Rx	ANY(%)	SEVERE(%)
Life-threatening	50–75	30
Moderate systemic	30–50	10
Cutaneous only		
Child	1–10	<3
Adult	10–20	<5
Large local	5–10	2

TABLE 15.3 RISK FACTORS ASSOCIATIONS

Increased risk of reaction in children with ST

    Age < 1 y

    Active AD

Increased risk of fatal reaction with ST

    Failure to do prick before ID testing

Increased risk of reactions to ST

    Asthma

    Female

Adverse reactions during VIT

    Increased with HB and W

    Build up > maintenance

    <AIT

    For FA increased with hx of ST reaction or LLR after WBE

    Maybe increased with rush

    Maybe decreased with ultra-rush

    MCAD

    Increased BST

β-Blockers/ACEI

Not increased frequency

Possibly more difficult to treat

Severe or fatal reactions to stings increases

Increased BST

Short (<5 min) onset

Older (>40 yr old)

Absence of urticaria/angioedema

Male

Comorbid cardiovascular disease

Head or neck sting site

Bee

Indolent systemic mastocytosis

Multiple or frequent stings inset

ACEI, angiotensin converting enzyme inhibitor; AD, atopic dermatitis; AIT, allergen immunotherapy; BST, baseline serum tryptase; HB, honeybee; ID, intra-dermal; LLR, large local reaction; MCAD, mast cell activation disease; ST, skin testing; VIT, venom immunotherapy; W, wasp; WBE, whole body extract.

Developed from Perkins JB, Yates AB. Pathologic findings in hymenoptera sting fatalities. In: Freeman TM, Tracy JM, eds. *Stinging Insect Allergy: A Clinician's Guide*.

Switzerland: Springer International Publishing; 2017:103–104; and Pesek R, Lockey RF. Adverse reactions to skin testing and immunotherapy with hymenoptera venoms and whole body extracts. In: Freeman TM, Tracy JM, eds. *Stinging Insect Allergy: A Clinician's Guide*. Switzerland: Springer International Publishing; 2017:136.

TABLE 15.4 WHEN TO OFFER IMMUNOTHERAPY IF A PATIENT HAS SPECIFIC IGE

Anaphylaxis after a sting	Always
Systemic cutaneous reaction after sting	When patient anxiety is high
Large local reactions	Frequent recurrences
MCAD	After a risk/benefit discussion

MCAD, mast cell activation disease.

The options for venom selection are straight forward. There is HB 100 µg/mL; W 100 µg/mL; YJ 100 µg/mL; YH 100 µg/mL; BFH 100 µg/mL; mixed vespid (MV) a mixture of YJ, BFH, and YH 300 µg/mL; and FA, single (*S. invicta*) 1:10 wt/vol and mixed (*S. invicta* and *S. richteri*) 1:10 wt/vol. One selects any of the venoms that are clinically important for which the patient has demonstrable IgE. MV is used whenever the patient needs two or three of the components (YJ, YH, BFH). HB is used for AHB. As *S. rictheri* is only found in small area of northern Alabama and Mississippi that border each other, the single component is usually used although the mixed variety is fine as well.

There are multiple regimens available for providing immunotherapy. Maintenance dose for VIT attempts to reach 100 mg (or 300 mg for MV). The maintenance dose for FA is 0.5 mL of full strength (full strength is a 1:10 dilution of the stock solution which is a 1:10 solution). Multiple schedules have been published (Table 15.5). Usually dosing starts several log concentrations below the intended maintenance dose at 0.05 mL. Dosing is advanced with each injection dose being 1 to 2/week. Options include clustering doses from the early vials on one visit delivering immunotherapy every half hour; rush where doses are given more frequently in order to reach maintenance dose within a few weeks; and ultra-rush where maintenance dose immunotherapy is reached within days of starting therapy. There may be greater risk for reactions with more

frequent dosing (42). However, several studies suggest comparable reaction rates (32,43).

Once maintenance is reached, the dose interval is usually extended to once per month. Then once q 2 months in the second year of maintenance. Studies have shown a three-month interval maintains protection, whereas a six-month interval does not (2).

Reactions that occur during immunotherapy can be as a result of the immunotherapy or as a result of another sting. Reactions can occur during build-up or once maintenance is reached. The suggested approach depends on both these conditions. If the patient has a field sting that results in anaphylaxis during build-up, the first question to address is: is the culprit the same as when they were stung before or not? If the patient is already on the correct therapy, the protocol needs to be continued to reach maintenance dose. If not or if unsure then repeat testing is indicated to see which venoms need to be added. If the patient has a reaction to an immunotherapy dose during build-up, this should be handled as any other immunotherapy reaction with the exception that stopping VIT should generally not be considered as the benefit–risk ratio is much higher for VIT than for routine allergen immunotherapy. If the patient has a field sting from the same insect species that leads to anaphylaxis while at maintenance dose or a reaction to VIT while at maintenance dose, it suggests VIT has "failed" to provide protection at the recommended maintenance dose. In either case, the maintenance dose should be increased as this has been shown to eventually give protection (44).

There are a variety of factors felt to influence the risk of reactions while on VIT. First, HB IT seems to have a higher failure rate than other VIT (8). Antihypertensive meds especially β-blockers and angiotensin converting enzyme inhibitors have clearly been associated with worse reactions in patients suffering an insect sting (40,45). Yet, several recent studies suggest that neither antihypertensive has much impact once patients are on immunotherapy (46–48). β-blockers still increase the difficulty of treating anaphylaxis if it should occur and are therefore relatively contra-indicated in patients needing VIT. Patients with elevated serum tryptase seem to be at increased risk of reactions and increased risk of severe reactions to field stings and to VIT (12). If a patient has suffered a very severe reaction to a field sting or to an immunotherapy dose, a serum tryptase should be ordered.

TABLE 15.5 REPRESENTATIVE BUILD-UP DOSING SCHEDULES

FOR FLYING HYMENOPTERA									FOR FIRE ANT					
CONVENTIONAL (61)			CLUSTER 30 MIN INTERVALS (62)			RUSH (63)			CONVENTIONAL (64)			RUSH 30 MIN INTERVALS (65)		
Week	µG/mL	Vol (mL)	Week	µG/mL	Vol (mL)	Day	µG/mL	Vol (mL)	Week	WT/VOL	Vol (mL)	Day	WT/VOL	Vol (mL)
1	1.0	0.05	1	0.01	0.1	1	0.1	0.1	1	1:100,000	0.05	1	1:100,000	0.3
2	1.0	0.1		0.1	0.1		1	0.1	2	1:100,000	0.15		1:10,000	0.1
3	1.0	0.2		1.0	0.1		10	0.1	3	1:100,000	0.25		1:10,000	0.3
4	1.0	0.4	2	1.0	0.1		100	0.1	4	1:100,000	0.5		1:1000	0.05
5	10	0.05		1.0	0.5		100	0.2	5	1:10,000	0.05		1:1000	0.15
6	10	0.1		10	0.1		100	0.4	6	1:10,000	0.1		1:1000	0.3
7	10	0.2	3	10	0.1		100	0.8	7	1:10,000	0.2		1:100a	0.05
8	10	0.4		10	0.5	2	100	1.0	8	1:10,000	0.3		1:100a	0.1
9	100	0.05		10	1.0				9	1:10,000	0.4		1:100a	0.2
10	100	0.1	4	100	0.1				10	1:10,000	0.5		1:100a	0.3
11	100	0.2		100	0.2				11	1:1,000	0.05	8	1:100	0.5
12	100	0.4	5	100	0.2				12	1:1,000	0.1			
13	100	0.6		100	0.3				13	1:1,000	0.2		Doses 60 min apart[a]	

14	100	0.8	6	100	0.3		14	1:1,000	0.3
15	100	1.0		100	0.3		15	1:1,000	0.4
			7	100	0.4		16	1:1,000	0.5
				100	0.4		17	1:100	0.05
			8	100	0.5		18	1:100	0.07
				100	0.5		19	1:100	0.1
			9	100	1.0		20	1:100	0.15
							21	1:100	0.2
							22	1:100	0.25
							23	1:100	0.4
							24	1:100	0.5

[a]Time between doses needs to be 60 minutes.

Modified from White K. Clinical aspects of hymenoptera allergy: IgE response, stings and immunotherapy. In: Freeman TM, Tracy JM, eds. *Stinging Insect Allergy: A Clinician's Guide*. Switzerland: Springer International Publishing; 2017:77–78.

While it is easy to tell when VIT has failed (a systemic reaction to the same insect while on VIT), it is much more difficult to predict when VIT is totally effective. Small studies looking at basophil histamine release showing correlation with sting challenges suggest that we might be able to monitor therapy in the future by this technique (27,29). A complete loss of specific IgE is clearly associated with decreased risk of reaction, but if immunotherapy is discontinued there is a tendency for specific IgE to recur. The overall risk in

several years appears to be greater than the general populations although not as high as someone who just had a systemic reaction (49). The only way to ensure VIT has been effective is to do a sting challenge or have a field sting occur. Unfortunately, even sting challenges are not perfect as natural history suggests that nearly half of insect stings in patients with known history and specific IgE result in no reaction, and sting challenges have considerable logistic and safety issues of their own (50). At this time, there is no definitive way to monitor therapy.

Several studies have suggested that it is reasonable to stop VIT after 3 to 5 years (49,51–53). Despite the recurrence of reactions in about 16.2% of patients 10 years after stopping VIT (49), it is reasonable to stop VIT in patients who have lost their specific IgE. Perhaps a more useful question is: when should VIT be continued? Patients who have established themselves as being at higher risk should be continued. Such patients include those with initial severe (life-threatening) reaction or those with reactions to immunotherapy either after a dose of VIT or after a field sting. Patients who may be at increased risk for severe reaction when not receiving immunotherapy such as patients being treated with β adrenergic blockers or angiotensin converting enzymes inhibitors, and patients with indolent systemic mastocytosis or elevated basal serum tryptase should also be considered for life-long therapy. Patients whose occupation increases the risk of exposure to stings, such as beekeepers and fire fighters, may also be considered for continuation.

REMAINING QUESTIONS

There remains many questions to be answered about hymenoptera hypersensitivity. The most current practice parameters suggest a variety of questions remain. These include determining a test for specific IgE that is both more sensitive and specific than our current tests. Recent improvements in *in vitro* testing have lowered the value that can be determined from 0.34 to 0.10 kU/L. While this might be expected to increase sensitivity, there might be a consequent loss of specificity making it a worse test and there is currently no data either way. Component testing and basophil histamine release assays may lead to improved results in the future but only if additional studies refine the technique (see earlier).

Skin testing itself could benefit from additional studies to examine whether the variety of values used to determine positive response actually has any clinical meaning. For example, do skin tests called positive at 0.001 µg/mL by 3 mm

wheal and flare greater than the histamine control all become positive with 5 to 10 mm flare and 10 to 20 mm flare by 1.0 µg/mL? Or is there any difference in the outcomes of patients called positive by different criteria? Would spiking our extracts with additional venom components or adding additional species to the currently available extracts improve our sensitivity (54,55)?

What is the risk for patients who suffered a systemic reaction in the distant past? We currently recommend VIT if those patients still have specific IgE, but there is no data specifying what the risk for these patients is. We know that without exposure to the specific antigen specific IgE decreases over time. We also know that in endemic areas many people will develop specific IgE to FA stings without a history of systemic reaction. So we could ask: if after a specified period of time (say 20 years) and a low specific IgE (say 0.34 kU/L or skin test positive only at 1.0 µg/mL), what is the risk of systemic reaction? If it is only slightly greater than the general population risk, should we still offer VIT?

Some studies have suggested that sublingual immunotherapy might reduce the risks of future stings (38,39). How long do the effects of sublingual immunotherapy persist?

Indolent systemic mastocytosis patients with very high levels of specific IgE do not seem to have the same risk of reaction to hymenoptera stings than those with lower levels (56). This suggests that there might be mast cell products that could be protective for patients with hymenoptera hypersensitivity. Could platelet-activating factor acetylhydrolase which we know down-regulates anaphylaxis be one such product (57)?

Despite our recommendation that patients can receive β adrenergic blockers with their VIT as the benefit of VIT is greater than the potential risk of anaphylaxis from treatment (2), we still have concerns about using β adrenergic blockers and giving immunotherapy especially if we need to use epinephrine. Is this risk reduced by using β_1 selective β blockers? Would it be safe to hold β adrenergic blockers for 24 hours before an immunotherapy dose?

There is evidence that using omalizumab may reduce the chance of reactions when giving immunotherapy even in patients with indolent systemic mastocytosis (58–60). We need well-designed studies to confirm its usefulness and to determine how long it needs to be continued once maintenance dose VIT is reached.

SUMMARY

VIT for flying hymenoptera or WB for FAs is an extremely effective prophylaxis for hymenoptera hypersensitive patients. Fortunately, this is not an extremely common cause of death or even frequent worrisome morbidity. Even though analysis suggests millions of individuals are at risk (2), most studies assess only a handful to a few hundreds of patients, which unfortunately hampers collecting the data we need to answer the many questions remaining.

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Erythema Multiforme, Stevens–Johnson Syndrome, and Toxic Epidermal Necrolysis

ANJU T. PETERS AND NEILL T. PETERS

Erythema multiforme (EM), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) are immunologically mediated diseases most often because of hypersensitivity to drugs or infections. It is well accepted that SJS and TEN represent varying severity of the same disease spectrum, with TEN being the most severe form, whereas EM is considered a separate entity (1,2). There is no uniformly accepted definition or classification of these diseases, and understanding of their exact immunologic basis is lacking.

HISTORICAL BACKGROUND

Erythema multiforme is a term originally attributed to Ferdinand von Hebra. In 1866, he wrote about "erythema exudativum multiforme," a single cutaneous eruption with multiple evolving stages of lesions (3). Von Hebra described EM as a mild cutaneous syndrome featuring symmetric acral lesions, which resolved without sequelae, and had a tendency to recur. In 1922, Stevens and Johnson described a generalized eruption in two children characterized by fever, erosive stomatitis, and severe ocular involvement (4). This eruption became known as Stevens–Johnson syndrome. Thomas, in 1950, proposed that the milder von Hebra form of EM be called "EM minor," and the more severe mucocutaneous eruption of SJS be called "EM major" (5). According to Thomas, fever and severe ocular involvement were the main points of distinction between the two types. The term "toxic epidermal necrolysis" was first introduced in 1956 by Lyell to describe patients with extensive epidermal necrosis that resembled scalded skin (6); it is occasionally referred to as Lyell's syndrome.

In 1993, an international consensus conference attempted to classify severe EM, SJS, and TEN, on the basis of skin lesions and the extent of epidermal

detachment (7). Using an illustrated atlas to standardize the diagnosis of acute severe bullous disorders attributed to drugs and infectious agents, the researchers defined bullous EM, SJS, SJS–TEN overlap, and TEN (Table 16.1). Considering SJS and TEN are rare, it has been difficult to create a universally accepted standard of care for the management of patients with these conditions. Nonetheless, several concepts regarding EM, SJS, and TEN and their therapy have been proposed.

ERYTHEMA MULTIFORME

EM, or the classic von Hebra EM, is a symmetric cutaneous eruption with a predilection for the extremities. The characteristic primary lesion is a "target" comprised of three zones (8) (Figs. 16.1 to 16.3). Centrally there is a disk surrounded by an elevated, pale ring. A zone of erythema then borders the pale ring. Mucosal involvement occurs in a majority of cases of EM; however, it is usually limited to the oral or ocular mucosa and typically is not severe (9,10). EM is often associated with herpes simplex virus (HSV) infections and follows an outbreak of HSV by 1 to 3 weeks (11,12). The eruption is self-limited, lasts 1 to 4 weeks, and requires *only* symptomatic management. HSV-induced EM may be recurrent, and in such cases, recurrences can be prevented with suppressive antiherpetic therapy (13,14). More severe variants of EM have also been described and are often caused by infections including HSV and *Mycoplasma pneumoniae* (2,15). Drugs may cause a small proportion of EM cases (16,17). Discontinuation of the implicated medication and supportive therapy results in complete resolution of the skin eruption in these cases. Short courses of oral corticosteroids have been used in treatment protocols with benefit without significant side effects (15). In some cases of EM, no obvious cause may be elicited (16).

TABLE 16.1 CLASSIFICATION OF ERYTHEMA MULTIFORME, STEVENS–JOHNSON SYNDROME, AND TOXIC EPIDERMAL NECROLYSIS

	SKIN LESIONS	EXTENT OF SKIN DETACHMENT (%)
Bullous erythema multiforme	Typical targets or raised atypical targets	<10
SJS	Erythematous or purpuric	<10

	macules or flat atypical targets	
Overlap SJS/TEN	Purpuric macules or flat atypical targets	10–30
TEN with spots	Purpuric macules or flat atypical targets	>30
TEN without spots	Detachment of large epidermal sheets without any targets	>10

SJS, Steven--Johnson syndrome; TEN, toxic epidermal necrolysis.

Adapted from Bastuji-Garin S, Rzany B, Stern RS, et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens–Johnson syndrome, and erythema multiforme. *Arch Dermatol.* 1993;129:92–96.

STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

SJS and TEN are severe, blistering mucocutaneous eruptions involving two or more mucosal surfaces, with or without visceral involvement (Figs. 16.4 to 16.6). Both SJS and TEN are rare, with an incidence of 1.89 cases/million people/year (18). Based on analysis of the 2009 to 2012 Nationwide Inpatient Sample, which is an approximately 20% stratified representative sample of all hospitalizations in the United States, the mean estimated incidences of SJS, SJS/TEN, and TEN were 9.2, 1.6, and 1.9/million adults/year (19). According to this study, the average age was 57.6 ± 0.4, 55.8 ± 0.9, and 59.6 ± 0.7 years for patients with SJS, SJS/TEN, and TEN, respectively. The majority of cases of SJS/TEN are attributed to drug exposures (16,18,20–24) (Table 16.2). Infections, especially with *M. pneumoniae,* are also known to produce SJS (25,26). Vaccines and viral infections such as varicella zoster virus have also been reported to cause SJS (27–29). The mortality for SJS is reported at <10%, and 30% mortality is associated with TEN. Both have significant morbidity and are associated with long-term complications (30,31). Most deaths are attributed to sepsis (32,33). In addition to the mortality associated with the acute hospitalization, patients with SJS and TEN have an increased risk of mortality

over the ensuing year with a mortality rate of 34% described at 1 year and 65% 5-year overall survival rate according to one study (34,35).

■ **FIGURE 16.1** Target lesion characteristic of erythema multiforme. (Courtesy of Dana Sachs, MD.)

The eruption classically starts 7 to 28 days after initiation of the drug. Reexposure of a sensitized individual to a drug that had previously induced SJS/TEN may result in an acute recurrence of the eruption in 1 to 2 days (36). Constitutional symptoms such as fever and malaise are often present and may occur with upper respiratory infection type symptoms that often precede the skin eruption (32). The eruption typically starts on the face and the upper torso and extends rapidly; individual lesions include flat, atypical targets with dusky centers and purpuric macules (Fig. 16.6) (7). Flaccid blisters also may form. SJS and TEN feature extensive mucosal involvement in >90% of patients. Oral, ocular, genitourinary, respiratory, and gastrointestinal mucosae, all may be involved, and therefore require appropriate evaluation (25,37,38). Nearly 69% to 81% of patients have ocular manifestations ranging from mild conjunctivitis to corneal ulcerations (9,39). The skin lesions may be painful and the epidermis may slough off in large sheets. Up to 10% of total body surface area (TBSA) epidermal detachment is classified as SJS, 10% to 30% detachment is classified as SJS/TEN overlap, and >30% as TEN (7). Nikolsky's sign that is characterized by detachment of the superficial skin by rubbing is present in involved areas of TEN.
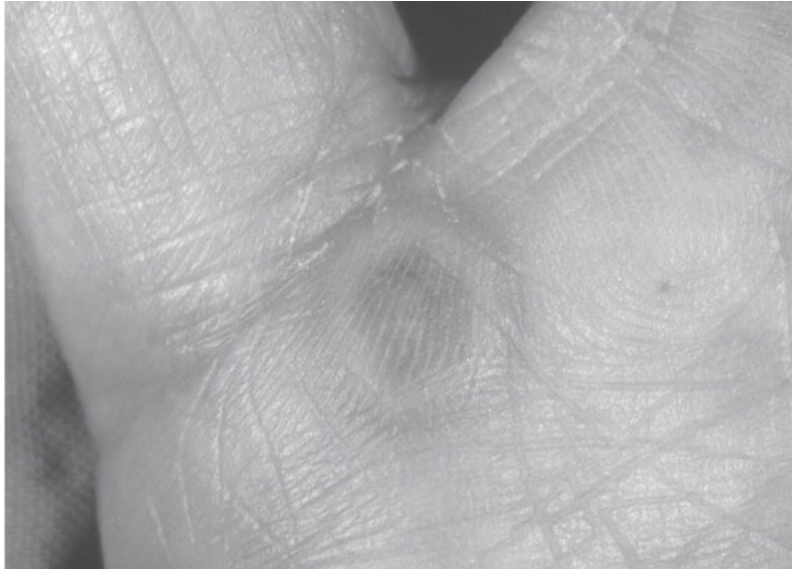
■ **FIGURE 16.2** Target lesion. (Courtesy of Dana Sachs, MD.)
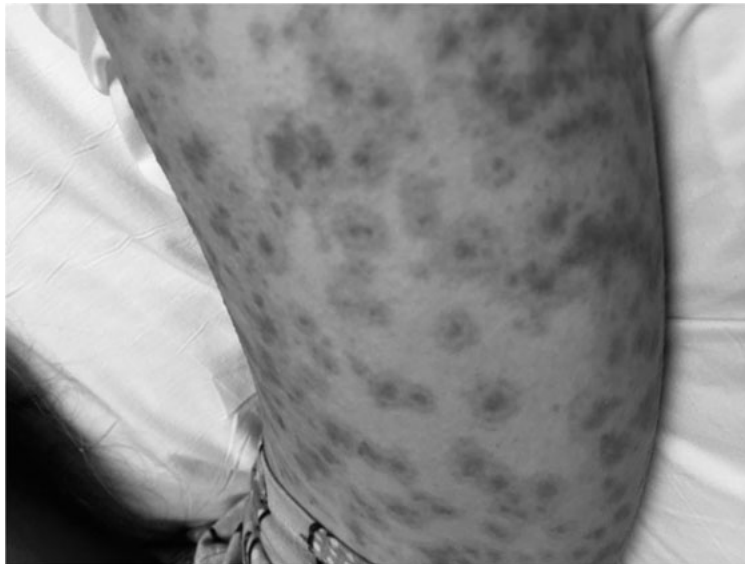
■ **FIGURE 16.3** Target lesion.

■ **FIGURE 16.4** Stevens–Johnson syndrome secondary to trimethoprim-sulfamethoxazole.

FIGURE 16.5 Stevens–Johnson syndrome. Same patient as shown in Fig. 16.4.

FIGURE 16.6 Purpuric macules classic of Stevens–Johnson syndrome.

TABLE 16.2 MEDICATIONS COMMONLY IMPLICATED IN STEVENS–JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Nevirapine	Allopurinol	Oxicam
Lamotrigine	Phenytoin	Nonsteroidal anti-Inflammatory agents
Sulfonamides	Phenobarbital	Penicillin
Carbamazepine	Chlormezanone	Cephalosporins
Fluoroquinolones	Valproic acid	Acetaminophen (paracetamol)

Data from references 16, 18, 21, 22, and 24.

The mucocutaneous findings in SJS and TEN are distinctive and recognizable by clinicians familiar with these conditions. Differential diagnostic considerations include staphylococcal scalded skin syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), severe acute graft versus host disease, acute generalized exanthematous pustulosis (AGEP), and paraneoplastic pemphigus. Skin biopsy for both routine histopathology and direct immunofluorescence can confirm a diagnosis of SJS/TEN and exclude other diagnostic considerations. The histopathology of EM, SJS, and TEN overlap. The main features are vacuolar interface dermatitis with apoptotic keratinocytes and superficial lymphohistiocytic infiltrates (40,41). All three conditions may feature vesiculation; however, only TEN features full-thickness necrosis of epidermal keratinocytes.

Treatment

Hospital admission is necessary in patients presenting with SJS/TEN. The extent of skin and mucosal involvement and laboratory findings need to be evaluated in emergency. The extent of epidermal detachment is considered both a prognostic factor and a guide to therapy (30). If >10% TBSA epidermal detachment is present, the patient has SJS/TEN overlap or TEN and requires different therapy (see discussion subsequently on Treatment of TEN). The laboratory investigation

should include a complete blood-cell count with differential, serum electrolytes, liver function tests, and urinalysis. The possible precipitating drug must be identified and discontinued immediately. If a patient is on multiple medications, all nonessential drugs should be discontinued. Early discontinuation of the etiologic drug has been reported to improve survival in patients with SJS and TEN (42). Ophthalmologic consultation should be obtained early in all patients with ocular involvement. Further diagnostic evaluation is dictated by the patient's condition, and other specialists may be necessary in the management of the patient depending on the organs involved by SJS/TEN. Dermatologists or plastic surgeons are the best specialists to manage the skin lesions associated with SJS/TEN. SCORe of toxic epidermal necrolysis (SCORTEN), a TEN-specific severity of illness score, utilizes independent variables to predict mortality in patients with SJS/TEN (Table 16.3) (43). Other studies have also confirmed that SCORTEN can be applied to predict mortality in SJS/TEN (44,45).

In addition to supportive care and removal of the potential precipitating cause, early use of systemic corticosteroids may be beneficial in SJS. For mild cases, oral prednisone at doses of 1 mg/kg/day may be sufficient (15,36). The dose of corticosteroids should be gradually reduced as the eruption resolves. An exacerbation of the eruption may occur if corticosteroids are withdrawn too rapidly. Intravenous methylprednisolone, at doses 500 to 1,000 mg a day, has reported benefit in a small case series of four patients with SJS and one patient with TEN (46). The use of systemic corticosteroids for SJS remains controversial with some groups reporting benefit with corticosteroids whereas others suggesting an increased risk of complications (38,47–51). In a series of patients with SJS, complete recovery was observed in all patients with SJS who were diagnosed early and in whom the precipitating cause was removed and corticosteroids were used promptly and in adequate doses (36–38,52). Of the 67 patients, three in the series died; however, their deaths were not attributable to either SJS or corticosteroid therapy (36–38).

TABLE 16.3 THE SCORTEN SCORING SYSTEM (BASED ON THE FIRST 24 HOURS OF ADMISSION)

Age > 40 y
History of malignancy

Heart rate > 120/minutes
Blood urea nitrogen > 27 mg/dL
Serum bicarbonate < 20 mEq/L
Serum glucose > 252 mg/dL
Epidermal detachment > 10% of body surface area at day 1

Mortality can be predicted by the total score: 0–1 points = 3.2%; 2 points = 12.1%; 3 points = 35.3%; 4 points = 58.3%; >5 points = 90% mortality.

Adapted from Bastuji-Garin S, Rouchard N, Bertocchi M, et al. SCORTEN: a severity of illness score for toxic epidermal necrolysis. *J Invest Dermatol*. 2000;114:149–153.

In general, systemic corticosteroid therapy has been avoided in TEN and has not been proved to be beneficial in the treatment of patients (53). An uncontrolled series of patients with SJS, SJS/TEN overlap, and TEN suggests reduced mortality with dexamethasone pulse therapy; however, this was based on a small study of 12 patients (51). Therapy for TEN is supportive. Patients with TEN need aggressive fluid and electrolyte correction, local skin care, and fastidious infection precautions. This is best achieved in a burn unit (53,54).

Intravenous immunoglobulin (IVIG) has been used in treatment of SJS and TEN with variable success. Some groups have shown reduction in healing time as well as improved survival (55–57). Others, however, have suggested no benefit with IVIG and, possibly, increased mortality (58–60). More recently, cyclosporine has been reported to improve outcomes in SJS/TEN in terms of reduction in predicted mortality and enhanced skin epithelialization (61–63). In small retrospective series, cyclosporine was superior to systemic corticosteroids and intravenous IgG replacement (62,63). These results are based on small series of patients, and at the present time, the use of cyclosporine is not universally accepted for the treatment of SJS/TEN.

Long-term sequelae from SJS and TEN can lead to significant morbidity. Chronic ocular disease is one of the most common long-term complications related to SJS and TEN, and patients need to be monitored for ocular complications. These can range from dryness, chronic and/or recurrent trichiasis,

corneal epithelial defects, corneal scarring and ulceration, and even blindness (64). Long-term complications can also involve other organ systems including cutaneous, pulmonary, and genitourinary organs (65–67). It is thus important to note that patients with SJS and TEN may require multidisciplinary care acutely for long term.

Pathogenesis

The exact immunologic basis for SJS and TEN is unknown. SJS/TEN is thought to occur through cell-mediated responses. CD8$^+$ T cells, the predominant cells found in the epidermis in bullous exanthems, SJS, and TEN, are thought to mediate keratinocyte destruction (68–71). Perforin, a cytoplasmic peptide found in cytotoxic T cells, has been detected in the dermis of SJS patients (72). Perforin can damage target cell membranes and therefore facilitate the entry of other granules such as granzymes into the target cell. These granules are known to trigger a series of reactions culminating in apoptosis (73). Histopathologic specimens from patients with SJS and TEN exhibit apoptosis (72,74).

Another mechanism involved in keratinocyte apoptosis in SJS and TEN involves the Fas–Fas ligand interactions. Studies have identified high concentrations of soluble Fas ligand in the sera of SJS/TEN patients (55,56,75). In addition to T cells, NK cells, dendritic cells, and macrophages have been implicated in the keratinocyte destruction characteristic of SJS/TEN (71,76,77). The mononuclear cells activate the T cells and also mediate keratinocyte destruction through the release of cytokines such as tumor necrosis factor α (78).

Genetic links have been described for severe drug reactions with strong associations between human leukocyte antigen (HLA) alleles and susceptibility to SJS/TEN. Initial studies identified an association with HLA-B*15:02 and carbamazepine-induced SJS/TEN in Asian populations (79). The study demonstrated that HLA-B*15:02 is specific for carbamazepine-induced activation of cytotoxic T cells implicated in the pathogenesis of SJS/TEN. Since then, HLA-B*15:02 and other HLA associations have been reported for drugs including allopurinol, lamotrigine, oxcarbazepine, and phenytoin (80–82).

■ CONCLUSION

SJS and TEN are severe cutaneous reactions most commonly caused by medications. Early recognition and withdrawal of the causative drug decreases the risk of death. Patients should be labeled allergic to the potential causative agent and counseled on strictly avoiding that drug in the future. Multidisciplinary

management of patients with SJS and TEN is important in improving clinical outcomes while reducing long-term morbidity and mortality.

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Drug Allergy

PART A

Introduction, Epidemiology, Classification of Adverse Reactions, Immunochemical Basis, Risk Factors, Evaluation of Suspected Drug Allergy, and Patient Management Considerations

ANNE M. DITTO

In the fifth edition of this book, the subject of drug allergy was extensively reviewed (1). Although a reasonably comprehensive overview of this important topic is addressed in the sixth and seventh editions (2) and in the current edition, an effort has been made to focus more sharply on clinically applicable information. An even more concise, practical review is published elsewhere (3). Other reviews of drug allergy are also recommended (4). Further, although specific recommendations are suggested regarding drug challenges and desensitization protocols, it is advisable, if possible, for those inexperienced in such matters to consult with physicians who regularly evaluate and manage hypersensitivity phenomena.

EPIDEMIOLOGY

A consequence of the rapid development of new drugs to diagnose and treat human illness has been the increased incidence of adverse reactions to these agents, which may produce additional morbidity and, on occasion, mortality. Their occurrence violates a basic principle of medical practice, primum non nocere (above all, do no harm). It is a sobering fact that adverse drug reactions are responsible for most iatrogenic illnesses. This should serve to remind physicians not to select potent and often unnecessary drugs to treat

inconsequential illnesses. Many patients have come to expect drug treatments for the most trivial of symptoms. On the other hand, a physician should not deprive a patient of necessary medication for fear of a reaction. Fortunately, most adverse reactions are not severe, but the predictability of seriousness is usually not possible in the individual case or with the individual drug.

An *adverse drug reaction* (ADR) may be defined as any undesired and unintended response that occurs at doses of an appropriate drug given for the therapeutic, diagnostic, or prophylactic benefit of the patient. The reaction should appear within a reasonable time after administration of the drug. This definition excludes therapeutic failure, which the patient may perceive as an ADR. A *drug* may be defined as any substance used in diagnosis, therapy, and prophylaxis of disease.

Although the exact incidence of ADRs is unknown, some estimates of their magnitude are available. Reported estimates of the incidence of ADRs leading to hospitalization vary, and this is complicated by inconsistency with definitions used, with methods used to collect and analyze data, and with some studies measuring prevalence while others measure incidence. A recent study based on an extensive literature search determined what proportion of hospital admissions was a result of ADRs (5). They reported that in developed countries, 6.3% of hospital admissions were due to ADRs, whereas in developing countries, 5.5% of admissions were for ADRs (5). A meta-analysis of 33 prospective studies from 1966 to 1996 in the United States showed that an incidence of 3.1% to 6.2% of hospital admissions was due to ADRs (6). Other studies from various countries, including Switzerland, Australia, and Germany, showed that ADRs were the reason for 2% to 6.1% of hospital admissions (7–11). As many as 15% to 30% of medical inpatients experience an ADR (12).

Severe cutaneous adverse drug reactions (SCARs), which include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS), occurs in approximately 2% of hospitalized patients (13). The incidence of SJS/TEN ranges from 2 to 7 cases/million/year (14), and the risk of death ranges from 5% to 10% in SJS to 50% in TEN (15). Drug-attributed deaths occur in 0.01% of surgical inpatients and in 0.14% to 0.17% of medical inpatients (7,10). Most of these fatalities occurred among patients who were terminally ill (16); in a study of ADR and hospital admissions in Australia, admissions for ADRs increased with patient age (10). Most deaths were caused by a small number of drugs that, by their nature, are known to be quite toxic:

anticoagulants, opioids, and immunosuppressants (13).

Information about outpatient ADRs is scant by comparison because most are not reported to pharmaceutic companies and appropriate national registries. Such surveys are complicated by the problem of differentiating between signs and symptoms attributable to the natural disease and those related to its treatment. ADRs may mimic virtually every disease, including the disease being treated. The challenge of monitoring ADRs is further complicated by multiple drug prescribing and the frequent use of nonprescription medications. Despite these limitations, such monitoring did identify the drug-induced skin rash that often follows ampicillin therapy.

Although most drug safety information is obtained from clinical trials before drug approval, premarketing studies are narrow in scope and thus cannot uncover ADRs in all patient populations. Adverse effects that occur over time or that are less frequent than 1 in 1,000, such as drug hypersensitivity, will not be detected until used by large numbers of patients after drug approval (17).

Thus, postmarketing surveillance is essential to the discovery of unexpected adverse drug effects. However, one estimate is that only 1% of ADRs are voluntarily reported to pharmaceutic companies and the US Food and Drug Administration (FDA) (18). In an attempt to ensure the timely collection of ADRs, the FDA introduced a simplified medical products reporting program in 1993, MedWatch (19). Although the FDA had an ADR reporting system in place before MedWatch, it was awkward to use and understandably discouraged health professionals' participation. Using MedWatch, the reporting individual does not have to prove absolutely an association between the drug and the adverse reaction. When reported, the information becomes part of a large database and can be investigated further. A simple, self-addressed, 1-page form is available and can be sent by mail, fax, or electronically (http://www.fda.gov/medwatch). The website also has an e-list where one can sign up to receive safety information reports directly by e-mail. Table 17A.1 summarizes how to report ADRs to MedWatch. Voluntary reporting led to the observation that ventricular arrhythmias, such as torsades de pointes, may occur when terfenadine is administered with erythromycin or ketoconazole (20).

Most ADRs do not have an allergic basis. What follows is a discussion that primarily focuses on those reactions that are, or possibly could be, mediated by immunologic mechanisms.

Allergic drug reactions account for 6% to 10% of all observed ADRs. It has been suggested that the risk of an allergic reaction is about 1% to 3% for most

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drugs. It is estimated that about 5% of adults may be allergic to one or more drugs. However, as many as 15% believe themselves to be or have been incorrectly labeled as being allergic to one or more drugs and, therefore, may be denied treatment with an essential medication. At times, it may be imperative to establish the presence or absence of allergy to a drug when its use is necessary and there are no safe alternatives. Although many patients with a history of reacting to a drug could safely receive that drug again, the outcome could be serious if that patient is truly allergic. Hence, a suspicion of drug hypersensitivity must be evaluated carefully.

TABLE 17A.1 REPORTING ADVERSE REACTIONS TO MEDWATCH

By Mail

• Use postage-paid MedWatch form 3500

By Phone

• 1-800-FDA-1088 to report by phone, to receive copies of form 3500 or a copy of *FDA Desk Guide for Adverse Event and Product Problem Reporting*

• 1-800-FDA-0178 to FAX report

• 1-800-FDA-7967 for a Vaccine Adverse Event Reporting System (VAERS) form for vaccines

By Internet

• http://www.fda.gov/medwatch

FDA, Food and Drug Administration.

CLASSIFICATION OF ADVERSE DRUG REACTIONS

Before proceeding with a detailed analysis of drug hypersensitivity, it is appropriate to attempt to place it in perspective with other ADRs. Physicians should carefully analyze ADRs to determine their nature because this will influence future use. For example, a drug-induced side effect may be corrected by simply reducing the dose. On the other hand, an allergic reaction to a drug may mean that drug cannot be used or may require special considerations before future administration.

ADRs may be divided into two major groups: (a) *predictable adverse reactions*, also called type A reactions, which are (i) often dose dependent, (ii) related to the known pharmacologic actions of the drug, (iii) occur in otherwise normal patients, and (iv) account for at least 80% of adverse drug effects; and (b) *unpredictable adverse reactions*, also called type B reactions, which are (i) usually dose independent, (ii) usually unrelated to the drug's pharmacologic actions, and (iii) often related to the individual's immunologic responsiveness or, on occasion, to genetic differences in susceptible patients.

Not included in this classification are those reactions that are unrelated to the drug itself but are attributable to events associated with and during its administration. Such events are often mistakenly ascribed to the drug, and the patient is inappropriately denied that agent in the future. Particularly after parenteral administration of a drug, *psychophysiologic reactions* in the form of hysteria, hyperventilation, or vasovagal response may ensue. Some of these reactions may be manifestations of underlying psychiatric disorders (21). Even anaphylactoid symptoms have been observed in placebo-treated patients (22). Another group of signs and symptoms is considered a *coincidental reaction*. They are a result of the disease under treatment and may be incorrectly attributed to the drug, for example, the appearance of viral exanthems and even urticaria during the course of a treatment with an antibiotic. Although it may be difficult to characterize a particular drug reaction, a helpful classification is shown in Table 17A.2, followed by a brief description of each.

Overdosage: Toxicity

The toxic effects of a drug are directly related to the systemic or local concentration of the drug in the body. Such effects are usually predictable on the basis of animal experimentation and may be expected in any patient provided a threshold level has been exceeded. Each drug tends to have its own characteristic toxic effects. Overdosage may result from an excess dose taken accidentally or deliberately. It may be due to accumulation as a result of some abnormality in the patient that interferes with normal metabolism and excretion of the drug. The toxicity of morphine is enhanced in the presence of liver disease (inability to detoxify the drug) or myxedema (depression of metabolic rate). The toxicity of chloramphenicol in infants is caused by immaturity of the glucuronide conjugating system, allowing a toxic concentration to accumulate. In the presence of renal failure, drugs such as the aminoglycosides, normally excreted by this route, may accumulate and produce toxic reactions.

TABLE 17A.2 CLASSIFICATION OF ADVERSE DRUG REACTIONS

PREDICTABLE ADVERSE REACTIONS OCCURRING IN NORMAL PATIENTS (TYPE A REACTIONS)

Overdosage: toxicity

Side effects
- Immediate expression
- Delayed expression

Secondary or indirect effects
- Drug related
- Disease associated

Drug–drug interactions

UNPREDICTABLE ADVERSE REACTIONS OCCURRING IN SUSCEPTIBLE PATIENTS (TYPE B REACTIONS)

Intolerance

Idiosyncratic reactions

Allergic (hypersensitivity) reactions

Pseudoallergic reactions

Side Effects

Side effects are the most frequent ADRs. They are therapeutically undesirable,

but often unavoidable, pharmacologic actions occurring at usual prescribed drug dosages. A drug frequently has several pharmacologic actions, and only one of those may be the desired therapeutic effect. The others may be considered side effects. The first-generation antihistamines commonly cause adverse central nervous system effects, such as sedation. Their anticholinergic side effects include dry mouth, blurred vision, and urinary retention.

Other side effects may be delayed in expression and include teratogenicity and carcinogenicity. Methotrexate, which has been used in some steroid-dependent asthmatic patients, is teratogenic and should not be used during pregnancy. Immunosuppressive agents can alter host immunity and may predispose the patient to malignancy (23).

Secondary or Indirect Effects

Secondary effects are indirect, but not inevitable, consequences of the drug's primary pharmacologic action. They may be interpreted as the appearance of another naturally occurring disease rather than being associated with administration of the drug. Some appear to be due to the drug itself, creating an ecologic disturbance and permitting the overgrowth of microorganisms. In the presence of antimicrobial (notably ampicillin, clindamycin, or cephalosporins) exposure, *Clostridium difficile* can flourish in the gastrointestinal tract in an environment in which there is reduced bacterial competition. Toxins produced by this organism may result in the development of pseudomembranous colitis (24).

Antimicrobial agents may be associated with another group of reactions that may mimic hypersensitivity, but appear to be disease associated. The *Jarisch–Herxheimer* phenomenon involves the development of fever, chills, headaches, skin rash, edema, lymphadenopathy, and often an exacerbation of preexisting skin lesions. The reaction is believed to result from the release of microbial antigens or endotoxins or both (25). This has usually followed penicillin treatment of syphilis and leptospirosis but has also been observed during treatment of parasitic and fungal infections. With continued treatment, the reaction subsides, thus confirming it is not an allergic response. Unfortunately, treatment is often discontinued and the drug blamed for the reaction. Another example would include the high incidence of skin rash in patients with the Epstein–Barr virus treated with ampicillin.

Drug–Drug Interactions

A drug–drug interaction is generally regarded as the modification of the effect of one drug by prior or concomitant administration of another. Fortunately, drug–drug interactions of major clinical consequence are relatively infrequent (26). It is also important to recall that not all drug interactions are harmful and that some may be used to clinical advantage.

An increase in the number of drugs taken concurrently increases the likelihood of an adverse drug interaction. When an interaction is reported, an average of between four and eight drugs are being taken by the patient. Therefore, elderly patients constitute the largest risk group, because they often receive polypharmacy. The danger of an interaction also escalates when several physicians are treating a patient, each for a separate condition. It is the physician's responsibility to determine what other medications the patient is taking, even nonprescription drugs.

Several widely prescribed agents used to treat allergic rhinitis and asthma interacted significantly with other drugs. The second-generation antihistamines, terfenadine and astemizole, were metabolized by cytochrome P-450 mixed-function oxidase enzymes. These antihistamines, in combination with drugs that inhibited the P-450 enzyme system, such as the imidazole antifungals ketoconazole and itraconazole or the macrolide antibiotics erythromycin and clarithromycin, resulted in increased concentrations of the antihistamines. This caused potential for prolongation of the QT interval, sometimes producing torsades de pointes or other serious cardiac arrhythmias (19). These antihistamines are no longer available in the United States. Although plasma concentrations of loratadine increased with concomitant administration of ketoconazole, this did not cause prolongation of the QT interval and the risk of torsades de pointes (27).

A number of drug–drug interaction programs are available online, including those hosted by WebMD and Medscape. Their accuracy is variable; using more than one program may improve the accuracy. Many electronic medical records (EMRs) show alerts not only for allergies but also when prescribing medications with possible interactions. However, this is limited to medications being prescribed or entered in the EMR. An excellent review of other adverse drug interactions may be found in a loose-leaf publication authored by Hansten and Horn (28).

Intolerance

Intolerance is a characteristic pharmacologic effect of a drug that is

quantitatively increased, and often is produced, by an unusually small dose of medication. Most patients develop tinnitus after large doses of salicylates and quinine, but few experience it after a single average dose or a smaller dose than usual. This untoward effect may be genetically determined and appears to be a function of the recipient, or it may occur in individuals lying at the extremes of dose–response curves for pharmacologic effects.

In contrast to intolerance, which implies a quantitatively increased pharmacologic effect occurring among susceptible individuals, *idiosyncratic and allergic reactions* are qualitatively aberrant and inexplicable in terms of the normal pharmacology of the drug given in usual therapeutic doses.

Idiosyncratic Reactions

Idiosyncrasy is a term used to describe a qualitatively abnormal, unexpected response to a drug, differing from its pharmacologic actions and thus resembling hypersensitivity. However, this reaction does not involve a proven, or even suspected, allergic mechanism.

A familiar example of an idiosyncratic reaction is the hemolytic anemia occurring commonly in African and Mediterranean populations and in 10% to 13% of African American males (sex-linked) exposed to oxidant drugs or their metabolites. About 25% of African American females are carriers, and only one-fifth of these have a sufficiently severe expression of the deficiency to be clinically important. A more severe form of the deficiency occurs in Caucasian Americans, primarily among people of Mediterranean origin. The erythrocytes of such individuals lack the enzyme glucose-6-phosphate dehydrogenase (G6PD) that is essential for aerobic metabolism of glucose and, consequently, cellular integrity (29). Although the original observations of this phenomenon were among susceptible individuals receiving primaquine, more than 50 drugs are known that induce hemolysis in G6PD-deficient patients. Clinically, the three classes of drugs most important in terms of their hemolytic potential are sulfonamides, nitrofurans, and water-soluble vitamin K analogues. If G6PD deficiency is suspected, simple screening tests dependent on hemoglobin oxidation, dye reduction, or fluorescence generation provide supporting evidence. The study of genetic G6PD deficiency and other genetic defects leading to ADRs has been termed *pharmacogenetics* (30).

Allergic Reactions

Allergic drug reactions occur in only a small number of individuals, are

unpredictable and quantitatively abnormal, and are unrelated to the pharmacologic action of the drug. Unlike idiosyncrasy, allergic drug reactions are the result of an immune response to a drug following previous exposure to the same drug or to an immunochemically related substance that had resulted in the formation of specific antibodies or sensitized T lymphocytes or both. Ideally, the term *drug allergy* or *hypersensitivity* should be restricted to those reactions proved, or more often presumed, to be the result of an immunologic mechanism.

The establishment of an allergic mechanism should be based on the demonstration of specific antibodies or sensitized lymphocytes or both. This is not often possible for many reactions ascribed to drug allergy. The diagnosis is usually based on clinical observations and, in selected instances, reexposure to the suspected agent under controlled circumstances. Even in the absence of direct immunologic evidence, an allergic drug reaction is often suspected when certain clinical and laboratory criteria are present, as suggested in Table 17A.3. Obviously, none of these are absolutely reliable (31).

Immediate reactions occurring within minutes often include manifestations of anaphylaxis. Accelerated reactions taking place after 1 hour to 3 days are frequently manifested as urticaria and angioedema and occasionally as other rashes, especially exanthems with fever. Delayed or late reactions do not appear until 3 days or longer after drug therapy is initiated and commonly include a diverse group of skin rashes, drug fever, and serum sickness–like reactions and, less commonly, hematologic, pulmonary, hepatic, and renal reactions, vasculitis, and a condition resembling lupus erythematosus.

Because clinical criteria are often inadequate, specific immunologic testing is desirable. Until this is accomplished, the relationship can at best be considered only presumptive. With few exceptions, safe, reliable *in vivo* tests and simple, rapid, predictable *in vitro* tests for the absolute diagnosis of drug allergy are unavailable. The most conclusive test is cautious readministration of the suspected drug, but usually the risk is not justified.

Pseudoallergic Reactions

Pseudoallergy refers to an immediate generalized reaction involving mast cell mediator release by an immunoglobulin E (IgE)-independent mechanism. Although the clinical manifestations often mimic or resemble IgE-mediated events (anaphylaxis), the initiating event does not involve an interaction between the drug or drug metabolites and drug-specific IgE antibodies. A receptor responsible for many pseudoallergic reactions has recently been identified; it is

the MAS-related G protein–coupled receptor X2 (MRGPRX2) (32). A difference is that these reactions may occur in patients without a previous exposure to these substances.

TABLE 17A.3 CLINICAL CRITERIA OF ALLERGIC DRUG REACTIONS

1. Allergic reactions occur in only a small percentage of patients receiving the drug and cannot be predicted from animal studies.

2. The observed clinical manifestations do not resemble known pharmacologic actions of the drug.

3. In the absence of prior exposure to the drug, allergic symptoms rarely appear before 1 week of continuous treatment. After sensitization, even years previously, the reaction may develop rapidly on reexposure to the drug. As a rule, drugs used with impunity for several months or longer are rarely the culprits. This temporal relationship is often the most vital information in determining which of many drugs being taken needs to be considered most seriously as the cause of a suspected drug hypersensitivity reaction.

4. The reaction may resemble other established allergic reactions, such as anaphylaxis, urticaria, asthma, and serum sickness–like reactions. However, a variety of skin rashes (particularly exanthems), fever, pulmonary infiltrates with eosinophilia, hepatitis, AIN, and lupus syndrome have been attributed to drug hypersensitivity.

5. The reaction may be reproduced by small doses of the suspected drug or other agents possessing similar or cross-reacting chemical structures.

6. Eosinophilia may be suggestive if present.

7. Rarely, drug-specific antibodies or T lymphocytes have been identified that react with the suspected drug or relevant drug metabolite.

8. As with ADRs in general, the reaction usually subsides within several days after discontinuation of the drug.

ADR, adverse drug reaction; AIN, acute interstitial nephritis.

Cationic peptides, such as ciprofloxacin, icatibant, and D-tubocurarine, bind MRGPRX2, causing release of mediators from mast cells, resulting in urticaria, angioedema, or even a clinical picture resembling anaphylaxis. Human β defensins and neuropeptides such as substance P are known to activate mast cells through MRGPRX2. In general, pseudoallergic reactions can be prevented by pretreatment with corticosteroids and antihistamines, as outlined for radiographic contrast media (RCM) (33). IgE-mediated allergic reactions, however, cannot.

Summary

The classification of ADRs presented here must be considered tentative. At times, it may be impossible to place a particular drug reaction under one of these headings. However, the common practice of labeling any ADR as "allergic" should be discouraged.

■ IMMUNOCHEMICAL BASIS OF DRUG ALLERGY

Drugs as Immunogens

The allergenic potential of drugs depends largely on their chemical properties. Increases in molecular size and complexity are associated with an increased ability to elicit an immune response. Hence, high-molecular-weight drugs, such as heterologous antisera, and recombinant proteins (e.g., infliximab and etanercept), streptokinase, L-asparaginase, and insulin, are complete antigens that can induce immune responses and elicit hypersensitivity reactions. Immunogenicity is weak or absent when substances have a molecular weight of less than 4,000 Da (34).

Most drugs are simple organic chemicals of low molecular weight, usually less than 1,000 Da. For such low-molecular-weight drugs to become immunogenic, the drug or a drug metabolite must be bound to a macromolecular carrier, often by covalent bonds, for effective antigen processing. The simple chemical (hapten), nonimmunogenic by itself, becomes immunogenic in the presence of the carrier macromolecule and now directs the specificity of the response.

β-Lactam antibiotics are highly reactive with proteins and can directly haptenate carrier macromolecules. However, most drugs are not sufficiently reactive to form a stable immunogenic complex. It is likely that haptens derived from most drugs are *reactive metabolites* of the parent compound, which then bind to carrier macromolecules to become immunogenic. This requirement for metabolic processing may help to explain the low incidence of drug allergy, the predisposition of certain drugs to cause sensitization because they are prone to form highly reactive metabolites, and the inability of skin testing and other immunologic tests with the unaltered drug to predict or identify the reaction as being allergic in nature.

Another model describing immunogenicity of low-molecular-weight compounds is the pharmacologic interactive (p-i) model in which nonreactive drugs form noncovalent bonds with major histocompatibility complex (MHC)

receptors and directly stimulate T cells (35,36). A third model proposed by Matzinger is the danger model, which states that an antigen presenting cell becomes activated when it receives "danger signals" from damaged or stressed cells, thus forming necessary co-stimulatory molecules and cytokines that propagate as well as determine the immunogenic response (37,38). Other proposed mechanisms include the "altered peptide repertoire," in which the drug binds to and alters the conformation of the self-peptide repertoire, which is then presented to human leukocyte antigen (HLA) and the T-cell receptor (TCR), eliciting a drug-specific T-cell response. The "altered TCR repertoire" model is one in which the drug binds to the TCR, altering its conformation and allowing it to bind HLA–self-peptide complex and eliciting an immune response. Another mechanism proposed specifically for SJS/TEN, in which granulysin plays a significant role, is the possible role of retinoids, which are thought to be released from the liver during initial injury from the drug, resulting in a type of hypervitaminosis A with resulting cytotoxicity and granulysin damage seen in SJS/TEN.

Penicillin allergy has received the most attention as a model of drug haptenization (39). Unfortunately, relevant drug haptens have not been identified for most allergic drug reactions. Studies of human IgE and IgG to sulfonamides have established the N^4-sulfonamidoyl determinant to be the major sulfonamide haptenic determinant (40).

It should be noted that an antigen must have multiple combining sites (multivalent) to elicit hypersensitivity reactions. This requirement permits bridging of IgE- and IgG-antibody molecules or antigen receptors on lymphocytes. Conjugation of the free drug or metabolite (hapten) with a macromolecular carrier to form a multivalent hapten-carrier conjugate is necessary to initiate an immune response and elicit a hypersensitivity reaction. The univalent ligand (free drug or metabolite), in large excess, may inhibit the response by competing with the multivalent conjugates for the same receptors. Therefore, the relative concentration of each will determine the frequency, severity, and rate of allergic drug reactions. Also, removal of haptens from carrier molecules by plasma enzymes (dehaptenation) will influence the likelihood of such reactions (41). Finally, some low-molecular-weight drugs, such as quaternary ammonium muscle relaxants and aminoglycosides, have enough distance between determinants to act as bivalent antigens without requiring conjugation to a carrier (42).

Immunologic Response to Drugs

Drugs often induce an immune response, but only a small number of patients actually experience clinical hypersensitivity reactions. For example, most patients exposed to penicillin and insulin develop demonstrable antibodies; however, in most instances, these do not result in allergic reactions or reduced effectiveness of the drug.

Mechanisms of Drug-induced Immunopathology

An immunologic response to any antigen may be quite diverse and the attendant reactions quite complex. Drugs are no exception and have been associated with all of the immunologic reactions proposed by Coombs and Gell (43) subsequently modified by Janeway (44) and Kay (45). It is likely that more than one mechanism may contribute to a particular reaction, but often one will predominate. Table 17A.4 is an attempt to provide an overview of the immunopathology of allergic drug reactions based on the original Coombs and Gell classification.

Penicillin alone has been associated with many of these reactions. Anaphylaxis and urticaria following penicillin administration are examples of type I reactions. The hemolytic anemia associated with high-dose penicillin therapy is a type II reaction. A serum sickness–like reaction, now most commonly associated with penicillin treatment, is a type III reaction. Finally, the contact dermatitis that occurred when penicillin was used topically in the past is an example of a type IV reaction.

◼ RISK FACTORS FOR DRUG ALLERGY

Several factors have been identified that may influence the induction of drug-specific immune responses and the elicitation of clinical reactions to these agents (46,47) (Table 17A.5).

TABLE 17A.4 IMMUNOPATHOLOGY OF ALLERGIC REACTIONS TO DRUGS

CLASSIFICATION	IMMUNOREACTANTS	CLINICAL PRESENTATION
Type I	Mast cell–mediated IGR • IgE dependent (anaphylactic) • IgE independent (pseudoallergic or anaphylactoid)	Anaphylaxis, urticaria, angioedema, asthma, rhinitis

Type IIa	Antibody-mediated cytotoxic reactions—IgG and IgM antibodies Complement often involved	Immune cytopenias Some organ inflammation
Type III	Immune complex–mediated reactions Complement involved	Serum sickness, vasculitis
Type IVa$_1$	T-lymphocyte–mediated reactions (CD4 and T$_H$1) type 1 cytokines (includes hapten model, p-i model, altered TCR or peptide repertoire)	Contact dermatitis Some exanthems

IgE, immunoglobulin E; IgM, immunoglobulin M; IGR, immediate generalized reactions; p-i, pharmacologic interactive; TCR, T-cell receptor.

Adapted from Kay AB. Concepts of allergy and hypersensitivity. In: Kay AB, ed. *Allergy and Allergic Diseases*. Oxford, UK: Blackwell Science, 1997:23.

Drug- and Treatment-Related Factors

Nature of the Drug

Macromolecular drugs, such as heterologous antisera and insulin, are complex antigens and have the potential to sensitize any patient. As noted earlier, most drugs have molecular weights of less than 1,000 Da and are not immunogenic by themselves. Immunogenicity is determined by the potential of the drug or, more often, a drug metabolite to form conjugates with carrier proteins.

β-Lactam antibiotics, aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), and sulfonamides account for 80% of allergic or pseudoallergic reactions.

Drug Exposure

Cutaneous application of a drug is generally considered to be associated with the greatest risk of sensitizing patients (47). In fact, penicillin, sulfonamides, and antihistamines are no longer used topically because of this potential. The adjuvant effect of some intramuscular preparations may increase the risk of sensitization; for example, the incidence of reactions to benzathine penicillin is higher than that to other penicillin preparations. The intravenous (IV) route may be the least likely to sensitize patients.

Once a patient is sensitized, the difference in reaction rates between oral and parenteral drug administration is likely related to the rate of drug administration. Anaphylaxis is less common after oral administration of a drug, although severe reactions have occurred. For other allergic drug reactions, the evidence supporting oral administration is less clear.

The dose and duration of treatment appear to affect the development of a drug-specific immunologic response. In drug-induced lupus erythematosus (DIL), the dose and duration of hydralazine therapy are important factors. Penicillin-induced hemolytic anemia follows high, sustained levels of drug therapy.

There is currently evidence that the frequency of drug administration affects the likelihood of sensitization (48). Thus, frequent courses of treatment are more likely to elicit an allergic reaction as is interrupted therapy. The longer the intervals between therapy, the less likely there will be an allergic reaction.

Patient-Related Factors

Age and Gender

There is a general impression that children are less likely than adults to become sensitized to drugs. However, serious allergic drug reactions do occur in children. Some confusion may arise in that the rash associated with a viral illness in children may incorrectly be ascribed to the administration of an antibiotic as treatment. Women are reported to have a higher incidence of ADRs than men (49,50).

Genetic Factors

Allergic drug reactions occur in only a small percentage of individuals treated with a given drug. It is likely that many factors, both genetic and environmental, are involved in determining which individuals in a large random population will develop an allergic reaction to a given drug.

TABLE 17A.5 RISK FACTORS FOR DRUG ALLERGY

DRUG- AND TREATMENT-RELATED FACTORS

Nature of the drug

    Immunologic reactivity

    Nonimmunologic activity

Drug exposure

    Route of administration

    Dose, duration, and frequency of treatment

PATIENT-RELATED FACTORS

Age and gender

Genetic factors

    Role of atopy

    Acetylator status

    Human leukocyte antigen type/single nucleotide polymorphisms

    Familial drug allergy

Prior drug reactions

    Persistence of drug-immune response

    Cross-sensitization

    Multiple drug allergy syndrome

Concurrent medical illness

    Asthma

    Cystic fibrosis

        Chronic kidney disease

        Cardiovascular disease

    Epstein–Barr viral infection

    Human immunodeficiency virus–infected patients

        Human herpesvirus 6 (HHV6) infection

        Coxsackievirus A6 infection

Concurrent medical therapy

β-Adrenergic receptor blocking agents

Patients with a history of allergic rhinitis, asthma, or atopic dermatitis (*the atopic constitution*) are not at increased risk for being sensitized to drugs compared with the general population (47). However, it does appear that atopic patients are more likely to develop pseudoallergic reactions, especially to RCM (51).

The rate of metabolism of a drug may influence the prevalence of sensitization. Individuals who are genetically *slow acetylators* are more likely to develop DIL associated with the administration of hydralazine and procainamide (52,53). Adverse reactions to sulfonamides may be more severe among slow acetylators (54).

Specific *HLA* genes have been associated with the risk of drug allergy. The susceptibility to drug-induced nephropathy in patients with rheumatoid arthritis treated with gold salts or penicillamine is associated with the HLA-DRw3 and HLA-B8 phenotypes, respectively (55). In addition, specific HLA genes have been associated with hydralazine-induced lupus erythematosus, levamisole-induced agranulocytosis, and sulfonamide-induced TEN (56). In a Han Chinese population, studies have shown a strong association between carbamazapime-induced SJS and HLA-B*1502 (57) as well as a strong association between HLA-B*5801 and severe cutaneous drug reactions (SJS and TEN) due to allopurinol (58). An association between HLA-B*5701 and hypersensitivity to abacavir, a potent reverse transriptase inhibitor, was shown in an HIV population in Western Australia (59). This has been confirmed in several other cohort studies (60–62); however, this association has not been found in black populations (61). Genetic risk may contribute not only to the severity of the reaction but also to the organs affected. HLA-A02:06 is associated with SJS/TEN with severe ocular complications (SOC) associated with cold medicine in Korean and Japanese populations but not Indian or Brazilian populations in whom SOC with cold medicine–induced SJS was associated with HLA-B44:03 (63,64). In addition, genome-wide association studies (GWAS) showed *IKZF1* single nucleotide polypmorhphisms (SNPs) significantly associated with the disease in the Japanese, Korean, and Indian populations with a trend found in the Brazilian population (65). GWAS have also identified SNPs associated with other drugs such as phenytoin-associated SCAR. These are CYP2C variants

linked to drug metabolism and thought to increase toxicity by reducing clearance (66). This is certainly plausible because higher doses or alterations in clearance have been shown to increase the risk of toxicity, as is seen with lamotrigine, which lead to changes in prescribing, initiating with low dose and slowly escalating (67).

In populations with a high risk of severe ADR, genetic testing has proved beneficial. Prior to being prescribed abacavir, testing for HLA-B57:01 was studied and shown to reduce the frequency of abacavir-associated hypersensitivity in Australia, the United Kingdom, and France (68,68a,68). Its cost-effectiveness was demonstrated in the United Kingdom, Spain, and other countries (69). Preventive genetic screening has also been shown to be effective in preventing SCAR associated with carbamazepine in Asians with HLA-B1502 allele (70) and, in those with HLA-B5801, allopurinol-induced SCAR. In fact, the US Department of Agriculture recommends screening for HLA-B1502 in those with Asian ancestry prior to administering carbamazepine (70), and in some hospitals, alerts are incorporated in the EMR, warning of the genetic association with hypersensitivity (71). As genetic screening costs continue to decline, and more and more genetic associations are found, this may be the most cost-effective way to identify patients at risk, reducing significant morbidity and mortality. A list of some known genetic associations can be found in Table 17A.6.

The possibility of *familial drug allergy* has been reported (56). Among adolescents whose parents had sustained an allergic reaction to antibiotics, 25.6% experienced an allergic reaction to an antimicrobial agent, whereas only 1.7% reacted when their parents tolerated antibiotics without an allergic reaction.

Prior Drug Reactions

Undoubtedly, the most important risk factor is a history of a prior hypersensitivity reaction to a drug being considered for treatment or one that may be immunochemically similar. However, drug hypersensitivity may not persist indefinitely. It is well established that, after an allergic reaction to penicillin, the half-life of antipenicilloyl IgE antibodies in serum ranges from 55 days to an indeterminate, long interval in excess of 2,000 days (47). Ten years after an immediate-type reaction to penicillin, only about 20% of individuals are still skin test positive.

There may be *cross-sensitization* between drugs. The likelihood of cross-reactivity among the various sulfonamide groups (antibacterials, sulfonylureas, and diuretics) is an issue that has not been resolved. There is little supporting

evidence in the medical literature that cross-sensitization is a significant problem. Patients who have demonstrated drug hypersensitivity in the past appear to have an increased tendency to develop sensitivity to new drugs. Penicillin-allergic patients have about a 10-fold increased risk of an allergic reaction to non–β-lactam antimicrobial drugs. The reactions were not restricted to immediate-type hypersensitivity. Fifty-seven percent reacted to a sulfonamide. With the exception of the aminoglycosides, reaction rates were much higher than expected in all other antibiotic classes, including erythromycin. Among children with multiple antibiotic sensitivities by history, 26% had positive penicillin skin tests. These observations suggest that such patients are prone to react to haptenating drugs during an infection, possibly because of the "danger" signals induced by infection. Obviously, such patients present difficult clinical management problems.

Concurrent Medical Illness

Although atopy does not predispose to the development of IgE-mediated drug hypersensitivity, it appears to be a risk factor for more severe reactions once sensitivity has occurred, especially in asthmatic patients (46,47). Children with cystic fibrosis are more likely to experience allergic drug reactions, especially during drug desensitization. In particular, they have a high incidence of piperacillin hypersensitivity and have been shown to have multiple haptens on circulating albumin as well as antigen-specific T cells (72). In a population-based study in Taiwan, chronic kidney disease (CKD) and cardiovascular disease (CVD) were associated with increased risk of hypersensitivity to allopurinol as was age > 60 with initial use, female sex, and dose > 100 mg/day (73). Mortality was also increased with CKD, CVD, and increased age. Clearance of the drug's metabolite, oxypurinol, was shown to be decreased in patients with CKD, and this may be one mechanism by which CKD and even dose and older age may contribute to increased risk (74).

Immune deficiency is associated with an increased frequency of ADRs, many of which appear to be allergic in nature. Patients who are immunosuppressed may become deficient in regulatory T lymphocytes that control IgE antibody synthesis.

Infection itself is associated with increased T-cell–mediated drug hypersensitivity.

Exanthematous rashes following the administration of ampicillin occur more frequently during Epstein–Barr viral infections (100% of children and 70% of adults) and among patients with lymphatic leukemia (68). Human herpesvirus 6

(HHV6) activation is associated with carbamazepine-induced DRESS (75), also known as drug-induced hypersensitivity syndrome (DIHS). Interestingly, idiosyncratic cutaneous disorders resembling ADRs, seen in occupational exposure to trichloroethylene were also shown to be associated with HHV6 (76). A recent study showed patients infected with a new variant of coxsackievirus A6 who presented with clinicopathologic features similar to SJS (77). ADRs, in particular hypersensitivity, occur with a much higher frequency among human immunodeficiency virus (HIV)–infected patients than among patients who are HIV seronegative. A retrospective study comparing *Pneumocystis carinii* pneumonia in patients with acquired immunodeficiency syndrome (AIDS) to a similar pneumonia in patients with other underlying immunosuppressive conditions reported adverse reactions to trimethoprim–sulfamethoxazole (TMP–SMX) in 65% of AIDS patients compared with 12% of patients with other immunosuppressive diseases, suggesting the abnormality may be due to the HIV infection. Slow acetylator phenotype is a risk factor for TMP–SMX in HIV-negative patients but not HIV-positive patients. TMP–SMX has been associated with rash, fever, and hematologic disturbances and, less frequently, with more severe reactions such as SJS, TEN, and anaphylactic reactions. Also, pentamidine, antituberculosis regimens containing isoniazid and rifampin, amoxicillin-clavulanate, and clindamycin have been associated with an increased incidence of ADRs, some of which may involve an allergic mechanism. It also appears that progression of HIV disease to a more advanced stage confers an increased risk of hypersensitivity reactions. It is thought that viruses may enhance ADRs through molecular mimicry, much like inducing autoimmune disease. Indeed, expansion of virus-specific cytotoxic T lymphocytes has been found in patients with drug hypersensitivity reactions (78).

TABLE 17A.6 ASSOCIATIONS OF ADR WITH HLA AND ETHNICITY

ETHNIC GROUP	DRUG	HLA	REACTION
Australian	Abacavir	B*57:01	Hypersensitivity
	Nevirapine	DRB1*01:01	MPE/DIHS
Cambodian	Abacavir	B*57:01	Hypersensitivity
European	Abacavir	B*57:01	Hypersensitivity

	Allopurinol	B*58:01	SJS/TEN/DIHS
	Carbamazepine	A*31:01	MPE/DIHS
	Oxicam	B*73, A*2, B*12	TEN
	Sulfamethoxazole	B*38	SJS/TEN
	Sulfonamide	A29, B12,DR7	TEN
French	Nevirapine	DRB1*01:01	MPE/DIHS
Han Chinese	Allopurinol	B*58:01	SJS/TEN/DIHS
	Carbamazepine	B*15:02	SJS/TEN
	Dapsone	B*15:11	SJS/TEN
	Oxcarbazepine	A*31:01	MPE/DIHS
	Phenytoin	B*13:01	DIHS
		B*15:02	SJS/TEN
		B*15:02	SJS/TEN
Indian	Carbamazepine	B*15:02	SJS/TEN
Japanese	Allopurinol	B*58:01	SJS/TEN/DIHS
	Carbamazepine	B*15:11	SJS/TEN
	Methazolamide	B*59:01	SJS/TEN
		A*31:01	SJS/TEN/DIHS
		B*59:01	SJS/TEN
		CW*01:02	SJS/TEN
Korean	Allopurinol	B*58:01	SJS/TEN/DIHS
	Carbamazepine	B*15:11	SJS/TEN
	Methazolamide	A*31:01	MPE/DIHS
		B*59:01	SJS/TEN
		CW*01:02	SJS/TEN
Malaysian	Carbamazepine	B*15:02	SJS/TEN

North American	Abacavir	B*57:01	Hypersensitivity
Sardinian	Nevirapine	B*14:02 Cw*08:01 Cw*08:02	Hypersensitivity
Thai	Abacavir Allopurinol Carbamazepine Nevirapine Phenytoin	B*57:01 B*58:01 B*15:02 B*35:05 B*15:02	Hypersensitivity SJS/TEN/DIHS SJS/TEN DIHS/MPE SJS/TEN
Other	Statins Clozapine Flucloxacillin Lumiracoxib Co-amoxiclav	DRB1*11:01 DQB1 B*57:01 DRB1*15:01	Autoimmune myopathy Agranulocytosis Hepatotoxicity Liver injury

ADR, adverse drug reaction; DIHS, drug-induced hypersensitivity syndrome; HLA, human leukocyte antigen; MPE, maculopapular exanthema; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Concurrent Medical Therapy

Some medications may alter the risk and severity of reactions to drugs. Patients treated with β-adrenergic blocking agents, even timolol maleate ophthalmic solution, may be more susceptible to, and prove to be more refractory to, treatment of drug-induced anaphylaxis, requiring greater fluid resuscitation and, possibly, more epinephrine to overcome the β-blockade.

CLINICAL CLASSIFICATION OF ALLERGIC REACTIONS TO DRUGS

A useful classification is based primarily on the clinical presentation or manifestations of such reactions. The presumption of allergy is based on clinical criteria cited earlier (Table 17A.3). Table 17A.7 provides an overview of a clinical classification based on organ systems involved; namely, generalized

multisystem involvement and predominantly organ-specific responses.

What follows is a brief discussion of each of these clinical entities, including a list of most commonly implicated drugs. Detailed lists of implicated drugs appear in periodic literature reviews (79).

Generalized or Multisystem Involvement

Immediate Generalized Reactions

The acute systemic reactions are among the most urgent of drug-related events. Greenberger has used the term *immediate generalized reactions* to underscore the fact that many are not IgE mediated. Drug-induced *anaphylaxis* should be reserved for a systemic reaction proved to be IgE mediated. Drug-induced *anaphylactoid reactions* are clinically indistinguishable from anaphylaxis but occur through IgE-independent mechanisms. Both ultimately result in the release of potent vasoactive and inflammatory mediators from mast cells and basophils.

TABLE 17A.7 CLINICAL CLASSIFICATION OF ALLERGIC REACTIONS TO DRUGS
GENERALIZED OR MULTISYSTEM INVOLVEMENT

Immediate generalized reactions
    Anaphylaxis (IgE-mediated reactions)
    Anaphylactoid reactions (IgE independent)

Serum sickness and serum sickness–like reactions
Drug fever

Drug-induced autoimmunity
    Reactions simulating systemic lupus erythematosus
    Other reactions

Hypersensitivity vasculitis
REACTIONS PREDOMINANTLY ORGAN SPECIFIC

Dermatologic manifestations[a]

Pulmonary manifestations
- Asthma
- Pulmonary infiltrates with eosinophilia
- Pneumonitis and fibrosis
- Noncardiogenic pulmonary edema

Hematologic manifestations
- Eosinophilia
- Drug-induced immune cytopenias
  - Thrombocytopenia
  - Hemolytic anemia
  - Agranulocytosis

Hepatic manifestations
- Cholestasis
- Hepatocellular damage
- Mixed pattern

Renal manifestations
- Glomerulonephritis
- Nephrotic syndrome
- Acute interstitial nephritis

Lymphoid system manifestations
- Pseudolymphoma
- Infectious mononucleosis–like syndrome

Cardiac manifestations

Neurologic manifestations

In a series of 32,812 continuously monitored patients, such reactions occurred in 12 patients (0.04%), and there were two deaths. Because anaphylaxis is more likely to be reported when a fatality occurs, its prevalence may be underestimated. Drug-induced anaphylaxis does not appear to confer increased risk of such generalized reactions to allergens from other sources (80).

Most reactions occur within 30 minutes, and death may ensue within minutes. In a retrospective study by Pumphrey in the United Kingdom investigating fatalities associated with anaphylaxis, more than one-half of the fatal reactions were iatrogenic. The majority of these reactions were caused by IV medications and took 5 minutes or less from the time of administration to the time of arrest (81). Anaphylaxis occurs most commonly after parenteral administration, but it has also followed oral, percutaneous, and respiratory exposure. Symptoms usually subside rapidly with appropriate treatment, but may last 24 hours or longer, and recurrent symptoms may appear several hours after apparent resolution of the reaction. As a rule, the severity of the reaction decreases with increasing time between exposure to the drug and onset of symptoms. Death is usually due to cardiovascular collapse or respiratory obstruction, especially laryngeal or upper airway edema. Although most reactions do not terminate fatally, the potential for such must be borne in mind, and the attending physician must respond immediately with appropriate treatment.

Table 17A.8 summarizes agents most frequently associated with immediate generalized reactions. In some situations, drugs, such as general anesthetic agents and vancomycin, which are primarily direct mast cell mediator releasers, can produce an IgE-mediated reaction (42,82). This distinction has clinical relevance in that IgE-independent reactions may be prevented or modified by pretreatment with corticosteroids and antihistamines, whereas such protection from drug-induced IgE-mediated reactions is less likely. In the latter situation, when the drug is medically necessary, desensitization is an option.

The β-lactam antibiotics, notably penicillin, are by far the most common causes of drug-induced anaphylaxis. Essentially all β-lactam anaphylactic reactions are IgE mediated. Immediate generalized reactions to other antibiotics occur but are relatively uncommon. Anaphylactoid reactions have been reported after the administration of ciprofloxacin and norfloxacin (83); as described earlier, these are likely due to MRGPRX2 binding (32).

TABLE 17A.8 DRUGS IMPLICATED IN IMMEDIATE GENERALIZED REACTIONS

ANAPHYLAXIS (IgE-MEDIATED)

β-Lactam antibiotics

Allergen extracts

Heterologous antisera

Insulin

Vaccines (egg based)

Streptokinase

Chymopapain

L-Asparaginase

Cisplatin

Carboplatin

Latex[a]

ANAPHYLACTOID (IgE-INDEPENDENT)

Radiocontrast material

Aspirin

Nonsteroidal anti-inflammatory drugs

Dextran and iron dextran

Anesthetic drugs

   Induction agents[b]

   Muscle relaxants[b]

Protamine[b]

Vancomycin[b]

Ciprofloxacin

Taxanes (i.e., paclitaxel)

Epipodophylotoxins (i.e., etoposide, teniposide)

[a]Not a drug *per se*, but often an important consideration in a medical setting.

Cancer chemotherapeutic agents have been associated with hypersensitivity reactions, most commonly type I immediate generalized reactions (84). L-Asparaginase has the highest risk for such reactions. Serious anaphylactic reactions with respiratory distress and hypotension occur in about 10% of patients treated. It is likely that most of these reactions are IgE mediated. However, skin testing appears to be of no value in predicting a reaction because there are both false-positive and false-negative results. Therefore, one must be prepared to treat anaphylaxis with each dose. For those reacting to L-asparaginase derived from *Escherichia coli*, one derived from *Erwinia chyoanthermia* (a plant pathogen) or a modified asparaginase (pegaspargase) may be a clinically effective substitute. Cisplatin and carboplatin are second only to L-asparaginase in producing such reactions. Skin testing with these agents appears to have predictive value, and desensitization has been successful when these drugs are medically necessary (85). The initial use of paclitaxel and other taxanes to treat ovarian and breast cancer was associated with a 10% risk for anaphylactoid reactions. However, with premedication and lengthening of the infusion time, the risk is significantly reduced (86). All other antitumor drugs, except altretamine, the nitrosoureas, and dactinomycin, have occasionally been associated with hypersensitivity reactions (84). Some appear to be IgE mediated, but most are probably IgE independent.

Anaphylactic and anaphylactoid reactions occurring during the perioperative period have received increased attention. The evaluation and detection of these reactions is complicated by the use of multiple medications and the fact that patients are often unconscious and draped, which may mask the early signs and symptoms of an immediate generalized reaction (87). During anesthesia, the only feature observed may be cardiovascular collapse (88) or airway obstruction. Cyanosis resulting from oxygen desaturation may be noted. One large multicenter study indicated that 70% of cases were caused by muscle relaxants and 12% were caused by latex (89). Other agents, such as IV induction drugs, plasma volume expanders (dextran), opioid analgesics and antibiotics, also require consideration (31). With the increased use of cardiopulmonary bypass surgery, the incidence of protamine-induced immediate life-threatening reactions has risen (90). Anaphylaxis to ethylene oxide–sterilized devices has been described; hence, such devices used during anesthesia could potentially cause anaphylaxis (91).

Psyllium seed is an active ingredient of several bulk laxatives, and has been responsible for asthma following inhalation and anaphylaxis after ingestion, particularly in atopic subjects (92). Anaphylactoid reactions following IV fluorescein may be modified by pretreatment with corticosteroids and antihistamines (93). Of patients reacting to iron dextran, 0.6% had a life-threatening anaphylactoid reaction (94). Anaphylactoid reactions may also be caused by blood and blood products through the activation of complement and the production of anaphylatoxins. Adverse reactions to monoclonal antibodies include immediate generalized manifestations, but the mechanism for such remains unclear (95). Most appear not to be IgE mediated (96) and protocols including rapid desensitization have been established for managing these reactions (97,98).

If one surveys the medical literature, one will find that virtually all drugs, including corticosteroids, tetracycline, cromolyn, erythromycin, and cimetidine, have been implicated in such immediate generalized reactions. However, these infrequent reports should not be a reason to withhold essential medication.

Serum Sickness and Serum Sickness–Like Reactions

Serum sickness results from the administration of heterologous (often equine) antisera and is the human equivalent of immune complex–mediated serum sickness observed in experimental animals (99). A serum sickness–like illness has been attributed to a number of nonprotein drugs, notably the β-lactam antibiotics. These reactions are usually self-limited and the outcome favorable, but H_1 blockers and prednisone may be needed.

With effective immunization procedures, antimicrobial therapy, and the availability of human antitoxins, the incidence of serum sickness has declined. Currently, heterologous antisera are still used to counteract potent toxins such as snake venoms, black widow and brown recluse spider venom, botulism, and gas gangrene toxins as well as to treat diphtheria and rabies. Equine and rabbit antisera, used as antilymphocyte or antithymocyte globulins and as monoclonal antibodies for immunomodulation and cancer treatment, may cause serum sickness (100). Serum sickness has also been reported in patients receiving streptokinase (101).

β-Lactam antibiotics are considered to be the most common nonserum causes of serum sickness–like reactions (102). One literature review did not support this assertion (103). In fact, such reactions appear to be quite infrequent, with an incidence of 1.8 per 100,000 prescriptions of cefaclor and 1 per 10 million for

amoxicillin and cephalexin (104). Other drugs occasionally incriminated include ciprofloxacin, metronidazole, streptomycin, sulfonamides, allopurinol, carbamazepine, hydantoins, methimazole, phenylbutazone, propanolol, and thiouracil. It should be noted that the criteria for diagnosis might not be uniform for each drug.

The onset of serum sickness typically begins 6 to 21 days after administration of the causative agent. The latent period reflects the time required for the production of antibodies. The onset of symptoms coincides with the development of immune complexes. Among previously immunized individuals, the reaction may begin within 2 to 4 days following administration of the inciting agent. The manifestations include fever and malaise, skin eruptions, joint symptoms, and lymphadenopathy.

There is no laboratory finding specific for the diagnosis of serum sickness or serum sickness–like reactions. Laboratory abnormalities may be helpful, if present. The erythrocyte sedimentation rate may be elevated, although it has been noted to be normal or low (102). There may be a transient leukopenia or leukocytosis during the acute phase (79,105). Plasmacytosis may occasionally be present; in fact, serum sickness is one of the few illnesses in which plasma cells may be seen in the peripheral blood (106). The urinalysis may reveal slight proteinuria, hyaline casts, hemoglobinuria, and microscopic hematuria. However, nitrogen retention is rare. Transaminases and serum creatinine may be transiently elevated (100).

Serum concentrations of C3, C4, and total hemolytic complement are depressed, providing some evidence that an immune complex mechanism is operative. These may rapidly return to normal. Immune complex and elevated plasma concentrations of C3a and C5a anaphylatoxins have been documented (107).

The prognosis for complete recovery is excellent. The symptoms may be mild, lasting only a few days, or quite severe, persisting for several weeks or longer.

Antihistamines control urticaria. If symptoms are severe, corticosteroids (e.g., prednisone, 40 mg/day for 1 week and then taper) are indicated. However, corticosteroids do not prevent serum sickness, as noted in patients receiving antithymocyte globulin (100). Skin testing with foreign antisera is routinely performed to avoid anaphylaxis with future use of foreign serum.

Drug Fever

Fever is a well-known drug hypersensitivity reaction. An immunologic mechanism is often suspected. Fever may be the sole manifestation of drug hypersensitivity and is particularly perplexing in a clinical situation in which a patient is being treated for an infection.

The height of the temperature does not distinguish drug fever, and there does not appear to be any fever pattern typical of this entity. Although a distinct disparity between the recorded febrile response and the relative well-being of the patient has been emphasized, clearly, such individuals may be quite ill with high fever and shaking chills. Drug fever may be the sole manifestation of a drug allergy but is commonly seen with other signs of drug hypersensitivity such as rash, elevated liver enzymes, and eosinophils.

Laboratory studies usually reveal leukocytosis with a shift to the left, thus mimicking an infectious process. Mild eosinophilia may be present. An elevated erythrocyte sedimentation rate and abnormal liver function tests are present in most cases.

The most consistent feature of drug fever is prompt defervescence, usually within 48 to 72 hours after withdrawal of the offending agent. Subsequent readministration of the drug produces fever, and occasionally chills, within a matter of hours.

In general, the diagnosis of drug fever is one of exclusion after eliminating other potential causes of the febrile reaction. Prompt recognition of drug fever is essential. If not appreciated, patients may be subjected to multiple diagnostic procedures and inappropriate treatment. Of greater concern is the possibility that the reaction may become more generalized with resultant tissue damage. Autopsies on patients who died during drug fever show arteritis and focal necrosis in many organs, such as the myocardium, lung, and liver.

Drug-Induced Autoimmunity

Drug-Induced Systemic Lupus Erythematosus

DIL is the most familiar drug-induced autoimmune disease, in part because systemic lupus erythematosus (SLE) remains the prototype of autoimmunity. DIL is termed *autoimmune* because of its association with the development of antinuclear antibodies (ANAs). However, these same autoantibodies are found frequently in the absence of frank disease. An excellent review of drug-induced autoimmunity appears elsewhere (108) as well as a comprehensive review of the medications implicated (109).

Convincing evidence for DIL first appeared in 1953 after the introduction of hydralazine for treatment of hypertension (110) although it was first described in 1945 associated with sulfadiazine (111). Procainamide-induced lupus was first reported in 1962 and is now the most common cause of DIL in the United States (112). These drugs have also been the best studied. Other agents for which there has been definite proof of an association include isoniazid, chlorpromazine, methyldopa, quinidine, and minocycline. Another group of drugs probably associated with the syndrome includes many anticonvulsants, β-blockers, antithyroid drugs, penicillamine, sulfasalazine, and lithium. There have been case reports of DIL associated with monoclonal antibodies such as inflixamab and etanercept (113,114), and an ANA-negative, antihistone-positive DIL has been described with lisinopril (115). There are case reports linking statins such as lovastatin, fluvastatin, and atorvastatin with DIL but with varying clinical manifestations, including pneumonitis, and cutaneous manifestations (116).

The incidence of DIL is not precisely known. In a recent survey of patients with lupus erythematosus seen in a private practice, 3% had DIL (117). The estimated incidence is 15,000 to 20,000 cases per year (118). In contrast to SLE, patients with DIL tend to be older, and males and females are equally affected (119). Patients with idiopathic SLE do not appear to be at increased risk from drugs implicated in DIL (120). Identified risk factors for developing DIL include HLA-DR4 (121), HLA-DR*0301 (122), slow acetlylator status (123), and complement C4 null allele (124).

Fever, malaise, arthralgias, myalgias, pleurisy, and slight weight loss may appear acutely in a patient receiving an implicated drug. Pleuropericardial manifestations, such as pleurisy, pleural effusions, pulmonary infiltrates, pericarditis, and pericardial effusions, are more often seen in patients taking procainamide. Unlike idiopathic SLE, the classic butterfly malar rash, discoid lesions, oral mucosal ulcers, Raynaud phenomenon, alopecia, and renal and central nervous system disease are unusual in DIL. Glomerulonephritis has occasionally been reported in hydralazine-induced lupus. As a rule, DIL is a milder disease than idiopathic SLE. Because many clinical features are nonspecific, the presence of ANAs (homogeneous pattern) or antihistone antibodies is essential in the diagnosis of drug-induced disease.

Clinical symptoms usually do not appear for many months after institution of drug treatment. Clinical features of DIL usually subside within days to weeks after the offending drug is discontinued. In an occasional patient, the symptoms may persist or recur over several months before disappearing. ANAs often

disappear in a few weeks to months but may persist for 1 year or longer. Mild symptoms may be managed with NSAIDs; more severe disease may require corticosteroid treatment.

If no satisfactory alternative drug is available and treatment is essential, the minimum effective dose of the drug and corticosteroids may be given simultaneously with caution and careful observation. With respect to procainamide, DIL can be prevented by giving *N*-acetylprocainamide, the major acetylated metabolite of procainamide. In fact, remission of procainamide-induced lupus has occurred when patients were switched to *N*-acetylprocainamide therapy (125,126). Finally, there are no data to suggest that the presence of ANAs necessitates discontinuance of the drug in asymptomatic patients. The low probability of clinical symptoms in seroreactors and the fact that major organs are usually spared in DIL support this recommendation (127).

Other Drug-Induced Autoimmune Disorders

In addition to DIL, D-penicillamine has been associated with several other autoimmune syndromes, such as myasthenia gravis, polymyositis and dermatomyositis, pemphigus and pemphigoid, membranous glomerulonephritis, Goodpasture's syndrome, and immune cytopenias (128). It has been suggested that by binding to cell membranes as a hapten, penicillamine could induce an autologous T-cell reaction, B-cell proliferation, autoantibodies, and autoimmune disorders (129).

Hypersensitivity Vasculitis

Vasculitis is a condition that is characterized by inflammation and necrosis of blood vessels. Organs or systems with a rich supply of blood vessels are most often involved. Thus, the skin is often involved in vasculitic syndromes. In the systemic necrotizing vasculitis group (polyarteritis nodosa, eosinophilic granulomatosis with polyangiitis) and granulomatous vasculitides (granulomatosis with polyangiitis, lymphomatoid granulomatosis, giant cell arteritides), cutaneous involvement is not as common a presenting feature as seen in the hypersensitivity vasculitides (HSV). Also, drugs do not appear to be implicated in the systemic necrotizing and granulomatous vasculitic syndromes.

Drugs appear to be responsible for or associated with a significant number of cases of HSV (130). These may occur at any age, but the average age of onset is in the fifth decade (131). The older patient is more likely to be taking medications that have been associated with this syndrome, for example, diuretics and cardiac drugs. Other frequently implicated agents include penicillin,

sulfonamides, thiouracils, hydantoins, iodides, and allopurinol. Allopurinol administration, particularly in association with renal compromise and concomitant thiazide therapy, has produced a vasculitic syndrome manifested by fever, malaise, rash, hepatocellular injury, renal failure, leukocytosis, and eosinophilia. The mortality rate approaches 25% (132). However, in many cases of HSV, no cause is ever identified. Fortunately, idiopathic cases tend to be self-limited.

The most common clinical feature of HSV is palpable purpura, and the skin may be the only site where vasculitis is recognized. The lesions occur in recurrent crops of varying size and number and are usually distributed in a symmetric pattern on the lower extremities and sacral area. Fever, malaise, myalgia, and anorexia may accompany the appearance of skin lesions. Usually, only cutaneous involvement occurs in drug-induced HSV, but glomerulonephritis, arthralgias or arthritis, abdominal pain and gastrointestinal bleeding, pulmonary infiltrates, and peripheral neuropathy are occasionally present.

The diagnosis of HSV is established by skin biopsy of a lesion demonstrating characteristic neutrophilic infiltrate of the blood vessel wall terminating in necrosis, leukocytoclasis (nuclear dust or fragmentation of nuclei), fibrinoid changes, and extravasation of erythrocytes. This inflammation involves small blood vessels, predominantly postcapillary venules. Recent studies indicate that in drug-induced vasculitis, multispecific antinuclear cytoplasmic antibody (ANCA) (ANCA positive to several neutrophil antigens) is commonly found. This is distinguished from ANCA to only one neutrophil antigen as is seen with idiopathic vasculitis and may serve to distinguish between the two (133).

When a patient presents with palpable purpura and has started a drug within the previous few months, consideration should be given to stopping that agent. Generally, the prognosis for HSV is excellent, and elimination of the offending agent, if one exists, usually suffices for therapy. For a minority of patients who have persistent lesions or significant involvement of other organ systems, corticosteroids are indicated.

Predominantly Organ-Specific Reactions

Dermatologic Manifestations

Cutaneous eruptions are the most frequent manifestations of ADRs and occur in 2% to 3% of hospitalized inpatients (134). The offending drug could be identified in most cases, and in one study was confirmed by drug challenges in

62% of patients (135). Frequently implicated agents include β-lactam antibiotics (especially ampicillin and amoxicillin), sulfonamides (especially TMP–SMX), NSAIDs, anticonvulsants, and central nervous system depressants (136).

Drug eruptions are most often exanthematous or morbilliform in nature. Most are of mild or moderate severity, often fade within a few days, and pose no threat to life or subsequent health. Much less common are SCARs, which include SJS, TEN, and drug-induced liver injury (DILI)/DRESS. These reactions, although rare, are responsible for significant morbidity and mortality. As noted earlier, some populations may be at higher risk for SCAR from certain medications based on HLA genotype. Typical features of a drug-induced eruption include an acute onset within 1 to 2 weeks after drug exposure (DILI/DRESS is more commonly delayed, occurring 4 to 6 weeks after initiation of the medication), symmetric distribution, predominant truncal involvement, brilliant coloration, and pruritus. Features that suggest that a reaction is serious include the presence of urticaria, blisters, mucosal involvement, facial edema, ulcerations, palpable purpura, fever, lymphadenopathy, and eosinophilia (137). The presence of these usually necessitates prompt withdrawal of the offending drug.

Table 17A.9 provides a list of recognizable cutaneous eruptions frequently induced by drugs, presumably on an immunologic basis.

Exanthematous or Morbilliform Eruptions

Exanthematous or morbilliform eruptions are the most common drug-induced eruptions and may be difficult to distinguish from viral exanthems. The rash may be predominantly erythematous, maculopapular, or morbilliform (measles-like), and often begins on the trunk or in areas of pressure, for example, the backs of bedridden patients. Pruritus is variable or minimal. Occasionally, pruritus may be an early symptom, preceding the development of cutaneous manifestations. Gold salts and sulfonamides have been associated with pruritus as an isolated feature. This rarely progresses to overt exfoliation, although this is possible (138). Usually, this drug-induced eruption appears within a week or so after institution of treatment. Unlike the generally benign nature of this ADR, a syndrome with a similar rash and fever, often with hepatitis, arthralgias, lymphadenopathy, and eosinophilia, has been termed *drug-induced hypersensitivity syndrome* (DIHS) (137), now referred to as drug rash with esoinophilia and systemic symptoms (DRESS) (139). It has a relatively later onset (2 to 6 weeks after initiation of treatment), evolves slowly, and may be difficult to distinguish from drug-induced vasculitis. Anticonvulsants, sulfonamides, and allopurinol are the most frequent causes of DRESS, although

other drugs such as antituberculous medication have been reported (140). Recovery is usually complete, but the rash and hepatitis may persist for weeks.

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TABLE 17A.9 DRUG-INDUCED CUTANEOUS MANIFESTATIONS

MOST FREQUENT

Exanthematous or morbilliform eruptions

Urticaria and angioedema

Contact dermatitis[a]

    Allergic eczematous contact dermatitis

    Systemic eczematous "contact-type" dermatitis

LESS FREQUENT

Fixed drug eruptions

Erythema multiforme–like eruptions

Stevens–Johnson syndrome (SJS)

Generalized exfoliative dermatitis

Photosensitivity

UNCOMMON

Purpuric eruptions

SCAR—Toxic epidermal necrolysis (Lyell syndrome), SJS, and drug-induced liver injury/drug reaction with eosinophilia and systemic symptoms (DILI/DRESS)

Erythema nodosum

Acute generalized exanthematous pustulosis

[a]Contact dermatitis is still listed among the top three, but there is evidence that this problem may be decreasing with the purposeful avoidance of topical sensitizers.

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Urticaria and Angioedema

Urticaria with or without angioedema is the second most frequent drug-induced eruption. It may occur alone or may be part of an immediate generalized reaction, such as anaphylaxis, or serum sickness. An allergic IgE-mediated

mechanism is often suspected, but it may be the result of a pseudoallergic reaction. One study reported that β-lactam antibiotics (through an allergic mechanism) accounted for one-third, and NSAIDs (through a pseudoallergic mechanism) accounted for another one-third, of drug-induced urticarial reactions (141).

Often, urticaria appears shortly after drug therapy is initiated, but its appearance may be delayed for days to weeks. Usually, individual urticarial lesions do not persist much longer than 24 hours, but new lesions may continue to appear in different areas of the body for 1 to 2 weeks. If the individual lesions last longer than 24 hours, or if the rash persists for much longer than 2 weeks, the possibility of another diagnosis such as urticarial vasculitis should be considered. A drug etiology should be considered in any patient with chronic urticaria, which is defined as lasting more than 6 weeks.

Angioedema is most often associated with urticaria, but it may occur alone. Angiotensin-converting enzyme (ACE) inhibitors are responsible for most cases of angioedema requiring hospitalization (142). The risk of angioedema is estimated to be between 0.1% and 0.2% in patients receiving such therapy (143). Patients with ididopathic angioedema are at increased risk of ACE inhibitor–induced angioedema, as are African Americans and women; therefore, caution should be used in treating these populations (144,145). The angioedema commonly involves the face and oropharyngeal tissues and may result in acute airway obstruction necessitating emergency intervention. Most episodes occur within the first week or so of therapy, but there are occasional reports of angioedema occurring years after initiation of treatment (146). The mechanism of angioedema is probably ACE inhibitor potentiation of bradykinin production (147), because icatibant has been reported to be a successful treatment (148). Angioedema has been reported with angiotensin II receptor blockers (ARBs) as well (149). Because treatment with epinephrine, antihistamines, and corticosteroids may be ineffective, the physician must be aware of the potential for airway compromise and the possible need for early airway intervention measures and treatment with icatibant (148). When angioedema follows the use of any one of these agents, treatment with any ACE inhibitor should be avoided. ARBs may be a good alternative. Angioedema has been reported with these, although the incidence is much lower (149).

Allergic Contact Dermatitis

Allergic contact dermatitis is produced by medications or by components of the drug delivery system applied topically to the skin and is an example of a type IV

cell-mediated immune reaction (Tables 17.4 and 17.9). Following topical sensitization, the contact dermatitis may be elicited by subsequent topical application. The appearance of the skin reaction and diagnosis by patch testing is similar to allergic contact dermatitis from other causes. The diagnosis should be suspected when the condition for which the topical preparation is being applied, such as eczema, fails to improve or worsens. Patients at increased risk of allergic contact dermatitis include those with stasis dermatitis, leg ulcers, perianal dermatitis, and hand eczema (150). Common offenders include neomycin, benzocaine, and ethylenediamine. Less common sensitizers include paraben esters, thimerosal, antihistamines, bacitracin, and, rarely, sunscreens and topical corticosteroids (151).

Neomycin is the most widely used topical antibiotic and has become the most sensitizing of all antibacterial preparations. Other aminoglycosides (e.g., streptomycin, kanamycin, gentamicin, tobramycin, amikacin, and netilmicin) may cross-react with neomycin, but this is variable (152). Neomycin-allergic patients may develop a systemic "contact-type" dermatitis when exposed to some of these drugs systemically. Many neomycin-allergic patients also react to bacitracin. In addition to neomycin, other topical antibiotics that are frequent sensitizers include penicillin, sulfonamides, chloramphenicol, and hydroxyquinolones. For this reason, they are seldom prescribed in the United States.

Benzocaine, a para-aminobenzoic acid (PABA) derivative, is the most common topical anesthetic associated with allergic contact dermatitis. It is found in many nonprescription preparations, such as sunburn and poison ivy remedies, topical analgesics, throat lozenges, and hemorrhoid preparations. In some benzocaine-sensitive patients, there may be cross-reactivity with other local anesthetics that are based on PABA esters, such as procaine, butacaine, and tetracaine. Suitable alternatives are the local anesthetics based on an amide structure, such as lidocaine, mepivacaine, and bupivacaine. Such individuals may also react to other para-amino compounds, such as some hair dyes (para-phenylenediamine), PABA-containing sunscreens, aniline dyes, and sulfonamides.

Ethylenediamine, a stabilizer used in some antibiotics, corticosteroids, and nystatin-containing combination creams, is a common sensitizer. Once sensitized to ethylenediamine topically, a patient may experience widespread dermatitis following the systemic administration of medicaments that contain ethylenediamine, such as aminophylline, hydroxyzine, and tripelennamine (153);

however, this is not common.

Among the less frequent topical sensitizers, paraben esters, used as preservatives in topical corticosteroid creams, were thought to be important; however, a recent study failed to support this assertion (154). Thimerosal is used topically as an antiseptic and also as a preservative. In one study, 7.5% of patients had a positive patch test with this material. Not all such patients are mercury allergic; many react to the thiosalicylic moiety. Local and even systemic reactions have been ascribed to thimerosal used as a preservative in some vaccines (155). However, if a patient's allergic history to thimerosal is topical sensitization only, skin testing to the vaccine followed by cautious test dosing may be considered. Systemic administration of antihistamines is rarely, if ever, associated with an allergic reaction; however, topical antihistamines are potential sensitizers, and their use should be avoided. Most instances of allergic contact dermatitis attributed to topical corticosteroids are due to the vehicle, not to the steroid itself. Patch testing with the highest concentration of the steroid ointment may help identify whether the steroid itself or the vehicle constituent is responsible. Some attention has already been focused on systemic eczematous contact-type dermatitis.

In summary, physicians should attempt to avoid or minimize the use of common sensitizers, such as neomycin and benzocaine, in the treatment of patients with chronic dermatoses, such as stasis dermatitis and hand eczema. A more comprehensive review of drug-induced allergic contact dermatitis is found elsewhere (156) and in Chapter 30.

Fixed Drug Eruptions

Fixed drug eruptions, in contrast to most other drug-induced dermatoses, are considered to be pathognomonic of drug hypersensitivity. Men are more frequently affected than women, and ages 20 to 40 are most common (157,158), but children may also be affected (159,160). The term *fixed* relates to the fact that these lesions tend to recur in the same sites each time the specific drug is administered. On occasion, the dermatitis may flare with antigenically related and even unrelated substances.

The characteristic lesion is well delineated and round or oval; it varies in size from a few millimeters to 25 to 30 cm. Edema appears initially, followed by erythema, which then darkens to become a deeply colored, reddish purple, dense raised lesion. On occasion, the lesions may be eczematous, urticarial, vesiculobullous, hemorrhagic, or nodular. Lesions are most common on the lips and genitals but may occur anywhere on the skin or mucous membranes

(161,162). Usually, a solitary lesion is present, but the lesions may be more numerous, and additional ones may develop with subsequent administration of the drug. The length of time from reexposure to the drug to the onset of symptoms is 30 minutes to 8 hours (mean, 2.1 hours). The lesions usually resolve within 2 to 3 weeks after drug withdrawal, leaving transient desquamation and residual hyperpigmentation.

The mechanism is unknown, but the histopathology is consistent with T-cell–mediated destruction of epidermal cells, resulting in keratinocyte damage (163). Studies point to a possible role for CD8$^+$ T-cell infiltration mediating keratinocyte apoptosis through a Fas–Fas ligand mechanism (164). Commonly implicated drugs include phenolphthalein, barbiturates, sulfonamides, tetracycline, and NSAIDs, although many drugs have been implicated, such as antifungals, antieleptics, narcotics, and many antibiotics (165). Drugs most commonly implicated vary depending on the country, the availability of drugs, and their pattern of use (166,167). In addition, some authors believe the location of lesions may be specific to the drug (168).

Treatment is usually not required after the offending drug has been withdrawn because most fixed drug eruptions are mild and not associated with significant symptoms. Corticosteroids may decrease the severity of the reaction without changing the course of the dermatitis (159).

Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis (AGEP) is an acute eruption of numerous small (less than 5 mm), sterile, mostly nonfollicular pustules in conjunction with fever more than 38°C and peripheral neutrophil count greater than 7×10^3/µL. The pustules are subcorneal or intraepidermal and appear on an erythematous, edematous base, and most commonly involve the trunk, upper extremities, and main skinfolds such as the neck, axilla, and groin. Transient renal failure and hypocalcemia are not uncommon (169). AGEP can be distinguished histologically from pustular psoriasis, and focal keratinocyte necrosis, vasculitis, perivascular eosinphils, as well as dermal edema can be seen on biopsy (170,171). AGEP is rare and for years was classified as pustular psoriasis and in 1968 was first thought to be a separate entity (172) and then better characterized in 1980 (173). Unlike pustular psoriasis, AGEP is most commonly caused by drug hypersensitivity, with antibiotics, in particular aminopenicillins, and diltiazem most commonly implicated (174). It is self-limited, with skin eruptions occurring soon after the medication is first administered (less than 2 days), followed by superficial desquamation and

spontaneous resolution in less than 15 days (171). AGEP is a predominantly neutrophilic inflammatory process in which drug-specific T cells have been found to play a role (175,176).

Erythema Multiforme–Like Eruptions

A useful classification for the heterogeneous syndrome of erythema multiforme has been suggested (177). Additional details can be found in Chapter 16. It is often a benign cutaneous illness with or without minimal mucous membrane involvement and has been designated *erythema multiforme minor* (EM minor). A more severe cutaneous reaction with marked mucous membrane (at least two mucosal surfaces) involvement and constitutional symptoms has been termed *erythema multiforme major* (EM major). SJS has become synonymous with EM major. In addition, some have considered TEN to represent the most severe form of this disease process, but others believe it should be considered a separate entity.

EM minor is a mild, self-limited cutaneous illness characterized by the sudden onset of symmetric erythematous eruptions on the dorsum of the hands and feet and on the extensor surfaces of the forearms and legs; palms and soles are commonly involved. Lesions rarely involve the scalp or face. Truncal involvement is usually sparse. The rash is minimally painful or pruritic. It is a relatively common condition in young adults 20 to 40 years of age and is often recurrent in nature. Mucous membrane involvement is usually limited to the oral cavity. Typically, the lesions begin as red, edematous papules that may resemble urticaria. Some lesions may develop concentric zones of color change, producing the pathognomonic "target" or "iris" lesions. The rash usually resolves in 2 to 4 weeks, leaving some residual postinflammatory hyperpigmentation but no scarring or atrophy. Constitutional symptoms are minimal or absent. The most common cause is believed to be herpes simplex infection, and oral acyclovir has been used to prevent recurrence of EM minor (178).

Most instances of drug-induced erythema multiforme result in more severe manifestations, classified as EM major or SJS. This bullous-erosive form can result in skin loss of up to 10% of the total body surface area (TBSA) and is often preceded by constitutional symptoms of high fever, headache, and malaise. Involvement of mucosal surfaces is a prominent and consistent feature. The cutaneous involvement is more extensive than in EM minor, and there is often more pronounced truncal involvement. Painful oropharyngeal mucous membrane lesions may interfere with nutrition. The vermilion border of the lips becomes denuded and develops serosanguinous crusts, a typical feature of this syndrome.

Eighty-five percent of patients develop conjunctival lesions, ranging from hyperemia to extensive pseudomembrane formation. Serious ocular complications include the development of keratitis sicca, corneal erosions, uveitis, and even bulbar perforation. Permanent visual impairment occurs in about 10% of patients. Mucous membrane involvement of the nares, anorectal junction, vulvovaginal region, and urethral meatus is less common. The epithelium of the tracheobronchial tree and esophagus may be involved, leading to stricture formation. EM major has a more protracted course, but most cases heal within 6 weeks (177). The mortality rate approaches 10% among patients with extensive disease. Sepsis is a major cause of death. Visceral involvement may include liver, kidney, or pulmonary disease.

The pathogenesis of this disorder is uncertain; however, the histopathologic features are similar to graft-versus-host disease and suggest an immune mechanism. Deposition of C3, IgM, and fibrin can be found in the upper dermal blood vessels (179). Upregulation of intercellular adhesion molecule 1, an adhesion molecule that facilitates recruitment of inflammatory cells, has been found in the epidermis of patients with erythema multiforme (180). However, unlike immune complex–mediated cutaneous vasculitis in which the cell infiltrate is mostly polymorphonuclear leukocytes, a mononuclear cell infiltrate (mostly lymphocytes) is present around the upper dermal blood vessels (181,182). Activated lymphocytes, mainly $CD8^+$ cells, are present, and there is increasing evidence that they are responsible for keratinocyte destruction (182–185). Epidermal apoptosis has also been reported in patients with SJS and TEN (182–186), and the role of the T cell in apoptosis is well established. It is possible that a drug or drug metabolite may bind to the cell surface, after which the patient then develops lymphocyte reactivity directed against the drug–cell complex.

Genetic susceptibility likely also plays a role. In a Han Chinese population, HLA-B*5801 was found to have a strong association with the development of SJS and TEN to allopurinol (58) and HLA-B*1502 with the development of SJS to carbamazapime (57). Other studies have shown a possible susceptibility to ocular involvement with HLA-Bw44 (part of HLA-B12) and HLA-oq81*0601 (187).

Drugs are the most common cause of SJS, accounting for at least half of cases (137). Drugs most frequently associated with this syndrome and also TEN include sulfonamides (especially TMP–SMX), anticonvulsants (notably carbamazepine), barbiturates, phenylbutazone, piroxicam, allopurinol, and

aminopenicillins. Occasional reactions have followed the use of cephalosporins, fluoroquinolones, vancomycin (188), antituberculous drugs, and NSAIDs, and proton pump inhibitors (PPIs) have been reported as a cause of SJS (189,190). Typically, symptoms begin 1 to 3 weeks after initiation of therapy.

Although there is some disagreement based on a series of 67 patients, early management of SJS with high-dose corticosteroids (160 to 240 mg methylprednisolone a day initially) should be implemented (191,192). Corticosteroids hastened recovery, produced no major side effects, and were associated with 100% survival and full recovery with no significant residual complications. This recommendation does not apply to the management of TEN. Drug challenges to establish whether a patient can safely tolerate a drug following a suspected reaction should not be considered with serious adverse reactions such as SJS, TEN, and exfoliative dermatitis.

Generalized Exfoliative Dermatitis

Exfoliative dermatitis is a serious and potentially life-threatening skin disease characterized by erythema and extensive scaling in which the superficial skin is shed over virtually the entire body. Even hair and nails are lost. Fever, chills, and malaise are often prominent, and there is a large extrarenal fluid loss. Secondary infection frequently develops, and on occasion, a glomerulonephritis has developed. Fatalities occur most often in elderly or debilitated patients. Laboratory tests and skin biopsy are helpful only to exclude other causes, such as psoriasis or cutaneous lymphoma. High-dose systemic corticosteroids and careful attention to fluid and electrolyte replacement are essential.

Exfoliative dermatitis may occur as a complication of preexisting skin disorders (e.g., psoriasis, seborrheic dermatitis, atopic dermatitis, and contact dermatitis); in association with lymphomas, leukemias, and other internal malignancies; or as a reaction to drugs. At times, a predisposing cause is not evident. The drug-induced eruption may appear abruptly or may follow an apparently benign, drug-induced exanthematous eruption. The process may continue for weeks or months after withdrawal of the offending drug.

Many drugs have been implicated in the development of exfoliative dermatitis, but the most frequently encountered are sulfonamides, penicillins, barbiturates, carbamazepine, phenytoin, phenylbutazone, allopurinol, and gold salts (193). No immunologic mechanism has been identified. The diagnosis is based on clinical grounds, the presence of erythema followed by scaling, and drug use compatible with this cutaneous reaction. The outcome is usually favorable if the causative agent is identified and then discontinued and

corticosteroids are initiated. However, an older study reported a 40% mortality rate, reminding us of the potential seriousness of this disorder (194).

Photosensitivity

Photosensitivity reactions are produced by the interaction of a drug present in the skin and light energy. The drug may be administered topically, orally, or parenterally. Although direct sunlight (ultraviolet spectrum 2,800 to 4,500 nm or 280 to 450 mm) is usually required, filtered or artificial light may produce reactions. African Americans have a lower incidence of drug photosensitivity, presumably because of greater melanin protection. The eruption is limited to light-exposed areas, such as the face, the V area of the neck, the forearms, and the dorsa of the hands. Often, a triangular area on the neck is spared because of shielding by the mandible. The intranasal areas and the groove of the chin are also spared. Although symmetric involvement is usual, unilateral distribution may result from activities such as keeping an arm out of the window while driving a car.

Photosensitivity may occur as a phototoxic nonimmunologic phenomenon and, less frequently, as a photoallergic immunologic reaction. Differential features are shown in Table 17A.10. Phototoxic reactions are nonimmunologic, occurring in a significant number of patients on first exposure when adequate light and drug concentrations are present. The drug absorbs light, and this oxidative energy is transferred to tissues, resulting in damage. The light absorption spectrum is specific for each drug. Clinically, the reaction resembles an exaggerated sunburn developing within a few hours after exposure. On occasion, vesiculation occurs, and hyperpigmentation remains in the area. Most phototoxic reactions are prevented if the light is filtered through ordinary window glass. Tetracycline, fluoroquinolones, and amiodarone are some of the many agents implicated in phototoxic reactions (195).

Photoallergic reactions, in contrast, generally start with an eczematous phase and more closely resemble contact dermatitis. Here, the radiant energy presumably alters the drug to form reactive metabolites that combine with cutaneous proteins to form a complete antigen, to which a T-cell–mediated immunologic response is directed. Such reactions occur in only a small number of patients exposed to the drug and light. The sensitization period may be days or months. The concentration of drug required to elicit the reaction can be very small, and there is cross-reactivity with immunochemically related substances. Flare-ups may occur at lightly covered or unexposed areas and at distant, previously exposed sites. The reaction may recur over a period of days or months

after light exposure, even without further drug administration. As a rule, longer ultraviolet light waves are involved, and window glass does not protect against a reaction. The photoallergic reaction may be detected by a positive photopatch test, which involves application of the suspected drug as an ordinary patch test for 24 hours, followed by exposure to a light source. Drugs implicated include the sulfonamides (antibacterials, hypoglycemics, and diuretics), phenothiazines, NSAIDs, and griseofulvin (196).

Purpuric Eruptions

Purpuric eruptions may occur as the sole expression of drug allergy, or they may be associated with other severe eruptions, notably erythema multiforme. Purpura caused by drug hypersensitivity may be due to thrombocytopenia.

TABLE 17A.10 DIFFERENTIAL FEATURES OF PHOTOSENSITIVITY

FEATURE	PHOTOTOXIC	PHOTOALLERGIC
Incidence	Common	Uncommon
Clinical picture	Sunburn-like	Eczematous
Reaction possible with first drug exposure	Yes	Requires sensitization period of days to months
Onset	4–8 h after exposure	12–24 h after exposure once sensitized
Chemical alteration of drug	No	Yes
Ultraviolet range	2,800–3,100 nm	3,200–4,500 nm
Drug dosages	Dose related	Dose independent once sensitized
Immunologic mechanism	None	T-cell mediated
Flares at distant previously	No	May occur

involved sites		
Recurrence from exposure to ultraviolet light alone	No	May occur in persistent eruptions

Simple, nonthrombocytopenic purpura has been described with sulfonamides, barbiturates, gold salts, carbromal, iodides, antihistamines, and meprobamate. Phenylbutazone has produced both thrombocytopenic and nonthrombocytopenic purpuras. The typical eruption is symmetric and appears around the feet and ankles or on the lower part of the legs, with subsequent spread upward. The face and neck are usually not involved. The eruption is composed of small, well-defined macules or patches of a reddish brown color. The lesions do not blanch on pressure and often are quite pruritic. With time, the dermatitis turns brown or grayish brown, and pigmentation may persist for a relatively long period. The mechanism of simple purpura is unknown.

A very severe purpuric eruption, often associated with hemorrhagic infection and necrosis with large sloughs, has been associated with coumarin anticoagulants. Although originally thought to be an immune-mediated process, it is now believed to be the result of an imbalance between procoagulant and fibrinolytic factors (197,198).

Toxic Epidermal Necrolysis

TEN (Lyell syndrome) induced by drugs is a rare, fulminating, potentially lethal syndrome characterized by the sudden onset of widespread blistering of the skin, extensive epidermal necrosis, and exfoliation of the skin involving more than 30% of the TBSA. *Overlap syndrome* (199) is the term used for a 10% to 30% loss associated with severe constitutional symptoms. It has been suggested that TEN may represent the extreme manifestation of EM major, but this position has been contested by others who cite the explosive onset of widespread blistering, the absence of target lesions, the peridermal necrosis without dermal infiltrates, and the paucity of immunologic deposits in the skin in TEN (200).

However, it has generally been assumed that TEN is an immunologically mediated disease because of its association with graft-versus-host disease, reports of immunoreactants in the skin, drug-dependent antiepidermal antibodies in some cases, and altered lymphocyte subsets in peripheral blood and the inflammatory infiltrate (200). An increased expression of HLA-B12 has been reported in TEN cases (56), and in a Han Chinese population, a very strong

association has been shown with HLA-B*5801 and SJS and TEN to allopurinol (58). High concentrations of soluble Fas ligand have been found in the sera of patients with TEN (201). Recent evidence suggests that Fas–FasL interaction on keratinocytes is responsible for apoptosis seen in TEN. Conserved levels of Fas are found on keratinocytes along with increased levels of bound FasL in lesional skin of patients with TEN. FasL on keratinocytes had been shown to be cytolytic in TEN and can be blocked with antibodies that interfere with Fas–FasL binding (201–203). TEN usually affects adults and is not to be confused with the staphylococcal scalded skin syndrome seen in children. The latter is characterized by a staphylococcal elaborated epidermolytic toxin, a cleavage plane high in the epidermis, and response to appropriate antimicrobial therapy. Features of TEN include keratinocyte necrosis and cleavage at the basal layer with loss of the entire epidermis (204). In addition, the mucosa of the respiratory and gastrointestinal tracts may be affected.

These patients are seriously ill with high fever, asthenia, skin pain, and anxiety. Marked skin erythema progresses over 1 to 3 days to the formation of huge bullae, which peel off in sheets, leaving painful denuded areas. Detachment of more than 30% of the epidermis is expected, whereas detachment of less than 10% is compatible with SJS (199), and 10% to 30% is considered overlap syndrome. A positive Nikolsky sign (i.e., dislodgment of the epidermis by lateral pressure) is present on erythematous areas. Mucosal lesions, including painful erosions and crusting, may be present on any surface. The complications of TEN and extensive thermal burns are similar. Unlike SJS, high-dose corticosteroids are of no benefit (191,192). Mortality may be reduced from an overall rate of 50% to less than 30% by early transfer to a burn center (205). Intravenous immunoglobulin (IVIG) contains antibodies to Fas and is therefore able to block Fas–FasL interaction (201). To date, most case reports of using IVIG in the treatment of TEN suggest that it may be beneficial clinically (206,207), particularly when used in doses greater than 2 g/kg (208). The drugs most frequently implicated in TEN include sulfonamides (20% to 28%; especially TMP–SMX), allopurinol (6% to 20%), barbiturates (6%), carbamazepine (5%), phenytoin (18%), and NSAIDs (especially oxyphenbutazone, 18%; piroxicam, isoxicam, and phenylbutazone, 8% each) (209,210).

Erythema Nodosum

Erythema nodosum–like lesions are usually bilateral, symmetric, ill-defined, warm, and tender subcutaneous nodules involving the anterior aspects (shins) of the legs. The lesions are usually red or sometimes resemble a hematoma and may

persist for a few days to several weeks. They do not ulcerate or suppurate, and usually resemble contusions as they involute. Mild constitutional symptoms of low-grade fever, malaise, myalgia, and arthralgia may be present. The lesions occur in association with streptococcal infections, tuberculosis, leprosy, deep fungal infections, cat scratch fever, lymphogranuloma venereum, sarcoidosis, ulcerative colitis, and other illnesses.

There is some disagreement as to whether drugs may cause erythema nodosum. Because the etiology of this disorder is unclear, its occurrence simultaneously with drug administration may be more coincidental than causative. Drugs most commonly implicated include sulfonamides, bromides, and oral contraceptives. Several other drugs, such as penicillin, barbiturates, and salicylates, are often suspected but seldom proved as causes of erythema nodosum. Treatment with corticosteroids is effective but is seldom necessary after withdrawal of the offending drug.

Pulmonary Manifestations

Bronchial Asthma

Pharmacologic agents are a common cause of acute exacerbations of asthma, which, on occasion, may be severe or even fatal. Drug-induced bronchospasm most often occurs in patients with known asthma but may unmask subclinical reactive airways disease. It may occur as a result of inhalation, ingestion, or parenteral administration of a drug. Although asthma may occur in drug-induced anaphylaxis or anaphylactoid reactions, bronchospasm is usually not a prominent feature; laryngeal edema is far more common, as is shock (81).

Airborne exposure to drugs during manufacture or during final preparation in the hospital or at home has resulted in asthma. Parents of children with cystic fibrosis have developed asthma following inhalation of pancreatic extract powder in the process of preparing their children's meals (211). Occupational exposure to some of these agents has caused asthma in nurses, for example, psyllium in bulk laxatives (212), and in pharmaceutic workers following exposure to various antibiotics (213). Spiramycin used in animal feeds has resulted in asthma among farmers, pet shop owners, and laboratory animal workers who inhale dusts from these products. NSAIDs account for more than two-thirds of drug-induced asthmatic reactions, with aspirin being responsible for more than half of these (214).

Both oral and ophthalmic preparations that block β-adrenergic receptors may induce bronchospasm among individuals with asthma or subclinical bronchial

hyperreactivity. This may occur immediately after initiation of treatment, or rarely after several months or years of therapy. Metoprolol, atenolol, and labetalol are less likely to cause bronchospasm than are propranolol, nadolol, and timolol (215). Timolol has been associated with fatal bronchospasm in patients using this ophthalmic preparation for glaucoma. Occasional subjects without asthma have developed bronchoconstriction after treatment with β-blocking drugs (216). One should also recall that β-blockers may increase the occurrence and magnitude of immediate generalized reactions to other agents (75), make resuscitation with epinephrine more difficult, and lead to larger volume loss.

Cholinesterase inhibitors, such as echothiophate ophthalmic solution used to treat glaucoma, and neostigmine or pyridostigmine used for myasthenia gravis, have produced bronchospasm. For obvious reasons, methacholine is no longer used in the treatment of glaucoma.

Although ACE inhibitors have been reported to cause acute bronchospasm or aggravate chronic asthma (217), a harsh, at times disabling, cough is a more likely side effect that may be confused with asthma. This occurs in 10% to 25% of patients taking these drugs, usually within the first 8 weeks of treatment, although it may develop within days or may not appear for up to 1 year (218). Switching from one agent to another is of no benefit. The cough typically resolves within 1 to 2 weeks after discontinuing the medication; persistence longer than 4 weeks should trigger a more comprehensive diagnostic evaluation. The mechanism of ACE inhibitor–induced cough is unclear. Cough may be avoided with the use of an ARB (219,220). As stated previously, ACE inhibitors may cause angioedema and may be a source of cough and dyspnea (221).

Sulfites and metabisulfites can provoke bronchospasm in a subset of asthmatic patients. The incidence is probably low but may be higher among those who are steroid dependent (222). These agents are used as preservatives to reduce microbial spoilage of foods, as inhibitors of enzymatic and nonenzymatic discoloration of foods, and as antioxidants that are often found in bronchodilator solutions. The mechanism responsible for sulfite-induced asthmatic reactions may be the result of the generation of sulfur dioxide from stomach acid, which is then inhaled. However, sulfite-sensitive asthmatic patients are not more sensitive to inhaled sulfur dioxide than are other asthmatic patients (223). The diagnosis of sulfite sensitivity may be established on the basis of sulfite challenge. There is no cross-reactivity between sulfites and aspirin (224). Bronchospasm in these patients may be treated with metered-dose inhalers or nebulized bronchodilator solutions containing negligible amounts of metabisulfites. Although epinephrine

contains sulfites, its use in an emergency situation even among sulfite-sensitive asthmatic patients should not be discouraged (223).

Pulmonary Infiltrates with Eosinophilia

An immunologic mechanism is probably operative in two forms of drug-induced acute lung injury, namely, hypersensitivity pneumonitis and pulmonary infiltrates associated with peripheral eosinophilia. Peripheral eosinophilia syndrome has been associated with the use of a number of drugs, including sulfonamides, penicillin, NSAIDs, methotrexate, carbamazepine, nitrofurantoin, phenytoin, cromolyn sodium, imipramine, and L-tryptophan (163). Although a nonproductive cough is the main symptom, headache, malaise, fever, nasal symptoms, dyspnea, and chest discomfort may occur. The chest radiograph may show diffuse or migratory focal infiltrates. Peripheral blood eosinophilia is usually present. Pulmonary function testing reveals restriction with decreased carbon dioxide diffusing capacity. A lung biopsy demonstrates interstitial and alveolar inflammation consisting of eosinophils and mononuclear cells. The outcome is usually excellent, with rapid clinical improvement on drug cessation and corticosteroid therapy. Usually, the patient's pulmonary function is restored with little residual damage.

Nitrofurantoin may also induce an acute syndrome, in which peripheral eosinophilia is present in about one-third of patients. However, this reaction differs from the drug-induced pulmonary infiltrates with peripheral eosinophilia syndrome just described because tissue eosinophilia is not present, and the clinical picture frequently includes the presence of a pleural effusion (225). Adverse pulmonary reactions occur in less than 1% of those taking the drug. Typically, the onset of the acute pulmonary reaction begins a few hours to 7 to 10 days after commencement of treatment. Typical symptoms include fever, dry cough, dyspnea (occasional wheezing), and, less commonly, pleuritic chest pain. A chest radiograph may show diffuse or unilateral involvement, with an alveolar or interstitial process that tends to involve lung bases. A small pleural effusion, usually unilateral, is seen in about one-third of patients. With the exception of DIL, nitrofurantoin is one of the only drugs producing an acute drug-induced pleural effusion. Knowledge of this reaction can prevent unnecessary hospitalization for suspected pneumonia. Acute reactions have a mortality rate of less than 1%. On withdrawal of the drug, resolution of the chest radiograph findings occurs within 24 to 48 hours.

Although the acute nitrofurantoin-induced pulmonary reaction is rarely fatal, a chronic reaction that is uncommon has a higher mortality rate of 8%. Cough

and dyspnea develop insidiously after 1 month or often longer of treatment. The chronic reaction mimics idiopathic pulmonary fibrosis clinically, radiologically, and histologically. Although somewhat controversial, if no improvement occurs after the drug has been withdrawn for 6 weeks, prednisone, 40 mg/day, should be given and continued for 3 to 6 months (225,226).

Of the cytotoxic chemotherapeutic agents, methotrexate is the most common cause of a noncytotoxic pulmonary reaction in which peripheral blood, but not tissue, eosinophilia may be present (227). In recent years, this drug has also been used to treat nonmalignant conditions, such as psoriasis, rheumatoid arthritis, and asthma. Symptoms usually begin within 6 weeks after initiation of treatment. Fever, malaise, headache, and chills may overshadow the presence of a nonproductive cough and dyspnea. Eosinophilia is present in 40% of cases. The chest radiograph demonstrates a diffuse interstitial process, and 10% to 15% of patients develop hilar adenopathy or pleural effusions. Recovery is usually prompt on withdrawal of methotrexate, but fatalities can occur. The addition of corticosteroid therapy may hasten recovery time. Although an immunologic mechanism has been suggested, some patients who have recovered may be able to resume methotrexate without adverse sequelae. Bleomycin and procarbazine, chemotherapeutic agents usually associated with cytotoxic pulmonary reactions, have occasionally produced a reaction similar to that of methotrexate.

Pneumonitis and Fibrosis

Slowly progressive pneumonitis or fibrosis is usually associated with cytotoxic chemotherapeutic drugs, such as bleomycin. However, some drugs, such as amiodarone, may produce a clinical picture similar to hypersensitivity pneumonitis without the presence of eosinophilia. In many cases, this category of drug-induced lung disease is often dose dependent.

Amiodarone, an important therapeutic agent in the treatment of many life-threatening arrhythmias, has produced an adverse pulmonary reaction in about 6% of patients, with 5% to 10% of these reactions being fatal (228). Symptoms rarely develop in a patient receiving less than 400 mg/day for less than 2 months. The clinical presentation is usually subacute with initial symptoms of nonproductive cough, dyspnea, and occasionally low-grade fever. The chest radiograph reveals an interstitial or alveolar process. Pulmonary function studies demonstrate a restrictive pattern with a diffusion defect. The sedimentation rate is elevated, but there is no eosinophilia. Histologic findings include the intra-alveolar accumulation of foamy macrophages, alveolar septal thickening, and occasional diffuse alveolar damage (229). Amiodarone has the unique ability to

stimulate the accumulation of phospholipids in many cells, including type II pneumocytes and alveolar macrophages. It is unclear whether these changes cause interstitial pneumonitis, because these findings are seen in most patients receiving this drug without any adverse pulmonary reactions. Although an immunologic mechanism has been suggested, the role of hypersensitivity in amiodarone-induced pneumonitis remains speculative (230). Most patients recover completely after cessation of therapy, although the addition of corticosteroids may be required. Further, when the drug is absolutely required to control a potentially fatal cardiac arrhythmia, patients may be able to continue treatment at the lowest dose possible when corticosteroids are given concomitantly (231).

Gold-induced pneumonitis is subacute in onset, occurring after a mean duration of therapy of 15 weeks and a mean cumulative dose of 582 mg (232). Exertional dyspnea is the predominant symptom, although a nonproductive cough and fever may be present. Radiographic findings include interstitial or alveolar infiltrates, whereas pulmonary function testing reveals findings compatible with a restrictive lung disorder. Peripheral blood eosinophilia is rare. Intense lymphocytosis is the most common finding in bronchoalveolar lavage. The condition is usually reversible after discontinuation of the gold injections, but corticosteroids may be required to reverse the process. Although this pulmonary reaction is rare, it must not be confused with rheumatoid lung disease.

Drug-induced chronic fibrotic reactions are probably nonimmunologic in nature, but their exact mechanism is unknown. Cytotoxic chemotherapeutic agents (azathioprine, bleomycin sulfate, busulfan, chlorambucil, cyclophosphamide, hydroxyurea, melphalan, mitomycin, nitrosoureas, and procarbazine hydrochloride) may induce pulmonary disease that is manifested clinically by the development of fever, nonproductive cough, and progressive dyspnea of gradual onset after treatment for 2 to 6 months or, rarely, years (233). It is essential to recognize this complication because such reactions may be fatal and could mimic other diseases, such as opportunistic infections. The chest radiograph reveals an interstitial or intra-alveolar pattern, especially at the lung bases. A decline in carbon monoxide diffusing capacity may even precede chest radiograph changes. Frequent early etiologic findings include damage to type I pneumocytes, which are the major alveolar lining cells, and atypia and proliferation of type II pneumocytes. Mononuclear cell infiltration of the interstitium may be seen early, followed by interstitial and alveolar fibrosis, which may progress to honeycombing. The prognosis is often poor, and the

response to corticosteroids is variable. Even those who respond to treatment may be left with clinically significant pulmonary function abnormalities. Although an immunologic mechanism has been suspected in some cases (234), it is now generally believed that these drugs induce the formation of toxic oxygen radicals that produce lung injury.

Noncardiogenic Pulmonary Edema

Another acute pulmonary reaction without eosinophilia is drug-induced noncardiogenic pulmonary edema. This develops very rapidly and may even begin with the first dose of the drug. The chest radiograph is similar to that caused by congestive heart failure. Hydrochlorothiazide is the only thiazide associated with this reaction (234). Most of the drugs associated with this reaction are illegal, including cocaine, heroin, and methadone (235,236). Salicylate-induced noncardiogenic pulmonary edema may occur when the blood salicylate level is over 40 mg/dL (237). In most cases, the reaction resolves rapidly after the drug is stopped. However, some cases may follow the clinical course of acute respiratory distress syndrome, notably with chemotherapeutic agents, such as mitomycin C or cytosine arabinoside (238), and rarely 2 hours after administration of RCM (239). The mechanism is unknown.

Hematologic Manifestations

Many instances of drug-induced thrombocytopenia and hemolytic anemia have been unequivocally shown by *in vitro* methods to be mediated by immunologic mechanisms. There is less certainty regarding drug-induced agranulocytosis. These reactions usually appear alone, without other organ involvement. The onset is usually abrupt, and recovery is expected within 1 to 2 weeks after drug withdrawal.

Eosinophilia

Eosinophilia may be present as the sole manifestation of drug hypersensitivity (240). More commonly, it is associated with other manifestations of drug allergy. Its recognition is useful because it may give early warning of hypersensitivity reactions that could produce permanent tissue damage or even death. However, most would agree that eosinophilia alone is not sufficient reason to discontinue treatment. In fact, some drugs, such as digitalis, may regularly produce eosinophilia, yet hypersensitivity reactions to this drug are rare.

Drugs that may be associated with eosinophilia in the absence of clinical disease include gold salts, allopurinol, aminosalicylic acid, ampicillin, tricyclic antidepressants, capreomycin sulfate, carbamazepine, digitalis, phenytoin,

sulfonamides, vancomycin, and streptomycin. There does not appear to be a common chemical or pharmacologic feature of these agents to account for the development of eosinophilia. Although the incidence of eosinophilia is probably less than 0.1% for most drugs, gold salts have been associated with marked eosinophilia in up to 47% of patients with rheumatoid arthritis and may be an early sign of an adverse reaction (241). Drug-induced eosinophilia does not appear to progress to a chronic eosinophilia or hypereosinophilic syndrome. However, in the face of a rising eosinophil count, discontinuing the drug may prevent further problems.

Thrombocytopenia

Thrombocytopenia is a well-recognized complication of drug therapy. The usual clinical manifestations are widespread petechiae and ecchymoses and occasionally gastrointestinal bleeding, hemoptysis, hematuria, and vaginal bleeding. Fortunately, intracranial hemorrhage is rare. On occasion, there may be associated fever, chills, and arthralgia. Bone marrow examination shows normal or increased numbers of normal-appearing megakaryocytes. With the exception of gold-induced immune thrombocytopenia, which may continue for months because of the persistence of the antigen in the reticuloendothelial system, prompt recovery within 2 weeks is expected on withdrawal of the drug (242). Fatalities are relatively infrequent. Readministration of the drug, even in minute doses, may produce an abrupt recrudescence of severe thrombocytopenia, often within a few hours.

Although many drugs have been reported to cause immune thrombocytopenia, the most common offenders in clinical practice today are quinidine, the sulfonamides (antibacterials, sulfonylureas, and thiazide diuretics), gold salts, and heparin.

The mechanism of drug-induced immune thrombocytopenia is thought to be the "innocent bystander" type. Shulman suggested the formation of an immunogenic drug–plasma protein complex to which antibodies are formed; this antibody–drug complex then reacts with the platelet (the innocent bystander), thereby initiating complement activation with subsequent platelet destruction (243). Some studies indicate that quinidine antibodies react with a platelet membrane glycoprotein in association with the drug (244). Patients with HLA-DR3 appear to be at increased risk for gold-induced thrombocytopenia.

Because heparin has had more widespread clinical use, the incidence of heparin-induced thrombocytopenia is about 5% (245). Some of these patients simultaneously develop acute thromboembolic complications. A heparin-

dependent IgG antibody has been demonstrated in the serum of these patients. A low-molecular-weight heparinoid can be substituted for heparin in patients who previously developed heparin-induced thrombocytopenia (246).

The diagnosis is often presumptive because the platelet count usually returns to normal within 2 weeks (longer if the drug is slowly excreted) after the drug is discontinued. Many *in vitro* tests are available at some centers to demonstrate drug-related platelet antibodies. A test dose of the offending drug is probably the most reliable means of diagnosis, but this involves significant risk and is seldom justified. Treatment involves stopping the suspected drug and observing the patient carefully over the next few weeks. Corticosteroids do not shorten the duration of thrombocytopenia but may hasten recovery because of their capillary protective effect. Platelet transfusions should not be given because transfused platelets are destroyed rapidly and may produce additional symptoms.

Hemolytic Anemia

Drug-induced immune hemolytic anemia may develop through three mechanisms: (1) immune complex type, (2) hapten or drug adsorption type, and (3) autoimmune induction (108). Another mechanism involves nonimmunologic adsorption of protein to the red blood cell membrane, which results in a positive Coombs test but seldom causes a hemolytic anemia. Hemolytic anemia after drug administration accounts for about 16% to 18% of acquired hemolytic anemias.

The *immune complex mechanism* accounts for most cases of drug-induced immune hemolysis. The antidrug antibody binds to a complex of drug and a specific blood group antigen, for example, Kidd, Kell, Rh, or Ii, on the red blood cell membrane (247). Drugs implicated include quinidine, chlorpropamide, nitrofurantoin, probenecid, rifampin, and streptomycin. Of note is that many of these drugs have also been associated with immune complex–mediated thrombocytopenia. The serum antidrug antibody is often IgM, and the direct Coombs test is usually positive.

Penicillin is the prototype of a drug that induces a hemolytic anemia by the *hapten or drug absorption mechanism* (248). Penicillin normally binds to proteins on the red blood cell membrane, and among patients who develop antibodies to the drug hapten on the red blood cell, a hemolytic anemia may occur. In sharp contrast to immune complex–mediated hemolysis, penicillin-induced hemolytic anemia occurs only with large doses of penicillin, at least 10 million units daily IV. Anemia usually develops after 1 week of therapy, more rapidly in patients with preexisting penicillin antibodies. The antidrug antibody

is IgG, and the red blood cells are removed by splenic sequestration independent of complement. About 3% of patients receiving high-dose penicillin therapy develop positive Coombs test results, but only some of these patients actually develop hemolytic anemia. The anemia usually abates promptly, but mild hemolysis may persist for several weeks. Other drugs occasionally associated with hemolysis by this mechanism include cisplatin and tetracycline.

Methyldopa is the most common cause of an *autoimmune* drug-induced hemolysis. A positive Coombs test develops in 11% to 36% of patients, depending on drug dosage, after 3 to 6 months of treatment (249). However, less than 1% of patients develop hemolytic anemia. The IgG autoantibody has specificity for antigens related to the Rh complex. The mechanism of autoantibody production is not clear. Hemolysis usually subsides within 1 to 2 weeks after the drug is stopped, but the Coombs test may remain positive for up to 2 years. These drug-induced antibodies will react with normal red blood cells. Because only a small number of patients actually develop hemolysis, a positive Coombs test alone is not sufficient reason to discontinue the medication. Several other drugs have induced autoimmune hemolytic disease, including levodopa, mefenamic acid, procainamide, and tolmetin.

A small number of patients treated with cephalothin develop a positive Coombs test as a result of *nonspecific adsorption of plasma proteins* onto red blood cell membranes. This does not result in a hemolytic anemia but may provide confusion in blood bank serology. Finally, several other drugs have been associated with hemolytic disease, but the mechanism is unclear. Such agents include chlorpromazine, erythromycin, ibuprofen, isoniazid, mesantoin, paraaminosalicylic acid, phenacetin, thiazides, and triamterene.

Agranulocytosis

Most instances of drug-induced neutropenia are due to bone marrow suppression, but they can also be mediated by immunologic mechanisms (250). The process usually develops 6 to 10 days after initial drug therapy; readministration of the drug after recovery may result in a hyperacute fall in granulocytes within 24 to 48 hours. Patients frequently develop high fever, chills, arthralgias, and severe prostration. The granulocytes disappear within a matter of hours, and this may persist 5 to 10 days after the offending drug is stopped. The role of drug-induced leukoagglutinins in producing the neutropenia has been questioned because such antibodies have also been found in patients who are not neutropenic. The exact immunologic mechanism by which some drugs induce neutropenia is unknown (251). Although many drugs have been

occasionally incriminated, sulfonamides, sulfasalazine, propylthiouracil, quinidine, procainamide, phenytoin, phenothiazines, semisynthetic penicillins, cephalosporins, and gold salts are more commonly reported offenders. After withdrawal of the offending agent, recovery is usual within 1 to 2 weeks, although it may require many weeks or months. Treatment includes the use of antibiotics and other supportive measures. The value of leukocyte transfusions is unclear. Hematopoietic growth factors appear to be of value (252).

Hepatic Manifestations

The liver is especially vulnerable to drug-induced injury because high concentrations of drugs are presented to it after ingestion and also because it plays a prominent role in the biotransformation of drugs to potentially toxic reactive metabolites. These reactive metabolites may induce tissue injury through inherent toxicity, or possibly on an immunologic basis (253). Drug-induced hepatic injury may mimic any form of acute or chronic hepatobiliary disease; however, these hepatic reactions are more commonly associated with acute injury.

Some estimates of the frequency of liver injury due to drugs are as follows (254):

- >2%: Aminosalicylic acid, troleandomycin, dapsone, and chenodeoxycholate

- 1% to 2%: Lovastatin, cyclosporine, and dantrolene

- 1%: Isoniazid and amiodarone

- 0.5% to 1%: Phenytoin, sulfonamides, and chlorpromazine

- 0.1% to 0.5%: Gold salts, salicylates, methyldopa, chlorpropamide, and erythromycin estolate

- <0.01%: Ketoconazole and contraceptive steroids

- <0.001%: Hydralazine and halothane

- <0.0001%: Penicillin, enflurane, and cimetidine

DILI caused by intrinsic toxicity of the drug or one of its metabolites is becoming less common. Such toxicity is often predictable because it is frequently detected in animal studies and during the early phases of clinical trials. A typical example of a drug producing such hepatotoxicity follows massive doses of acetaminophen (255). The excess acetaminophen is shunted into the cytochrome P-450 system pathway, resulting in excess formation of the reactive metabolite that binds to subcellular proteins, which in turn leads to

cellular necrosis.

Although there is little direct evidence that an immunologic mechanism (hepatocyte-specific antibodies or sensitized T lymphocytes) is operative in drug-induced hepatic injury, such reactions are often associated with other hypersensitivity features. Injury attributed to hypersensitivity is suspected when there is a variable sensitization period of 1 to 5 weeks; when the hepatic injury is associated with clinical features of hypersensitivity such as seen with DRESS; when histologic features reveal an eosinophil-rich inflammatory exudate or granulomas in the liver; when hepatitis-associated antigen is absent; and when there is prompt recurrence of hepatic dysfunction following the readministration of small doses of the suspected drug (not usually recommended). After withdrawal of the offending drug, recovery is expected unless irreversible cell damage has occurred. Such liver injury may take the form of cholestatic disease, hepatocellular injury or necrosis, or a mixed pattern.

Drug-induced cholestasis is most often manifested by icterus, but fever, skin rash, and eosinophilia may also be present. The serum alkaline phosphatase levels are often elevated 2 to 10 times normal, whereas the serum aminotransferases are only minimally increased. Occasionally, antimitochondrial antibodies are present. Liver biopsy reveals cholestasis, slight periportal mononuclear and eosinophilic infiltration, and minimal hepatocellular necrosis. After withdrawal of the offending drug, recovery may take several weeks. Persistent reactions may mimic primary biliary cirrhosis; however, antimitochondrial antibodies are usually not present. The most frequently implicated agents are the phenothiazines (particularly chlorpromazine), the estolate salt of erythromycin, and, less frequently, nitrofurantoin and sulfonamides (256).

Drug-induced hepatocellular injury mimics viral hepatitis but has a higher morbidity rate. In fact, 10% to 20% of patients with fulminant hepatic failure have drug-induced injury. The serum aminotransferases are increased, and icterus may develop, the latter associated with a higher mortality rate. The histologic appearance of the liver is not specific for drug-induced injury. Drugs commonly associated with hepatocellular damage are halothane, isoniazid, phenytoin, methyldopa, nitrofurantoin, allopurinol, and sulfonamides. It is now clear that damage from isoniazid is due to metabolism of the drug to a toxic metabolite, acetylhydrazine (257).

Only halothane-induced liver injury has reasonably good support for an immune-mediated process, primarily on the basis of finding circulating

antibodies that react with halothane-induced hepatic neoantigen in a significant number of patients with halothane-induced hepatitis (258). In the United States, enflurane and isoflurane have largely replaced halothane (except in children) because the incidence of hepatic injury appears to be less. However, cross-reacting antibodies have been identified in some patients (259).

Mixed pattern disease denotes instances of drug-induced liver disease that do not fit exactly into acute cholestasis or hepatocellular injury. There may be moderate abnormalities of serum aminotransferases and alkaline phosphatase levels with variable icterus. Among patients with phenytoin-induced hepatic injury, the pattern may resemble infectious mononucleosis with fever, lymphadenopathy, lymphoid hyperplasia, and spotty necrosis. Granulomas in the liver with variable hepatocellular necrosis are a hallmark of quinidine-induced hepatitis (260). Other drugs associated with hepatic granulomas are sulfonamides, allopurinol, carbamazepine, methyldopa, and phenothiazines.

Drug-induced chronic liver disease is rare but may also mimic any chronic hepatobiliary disease. Drug-induced chronic active hepatitis has been associated with methyldopa, isoniazid, and nitrofurantoin (261). Some of these patients may develop antinuclear and smooth muscle antibodies. Also, the chronic liver injury may not improve after withdrawal of the offending drug.

Renal Manifestations

The kidney is especially vulnerable to drug-induced toxicity because it receives, transports, and concentrates within its parenchyma a variety of potentially toxic substances. Tubular necrosis may follow drug-induced anaphylactic shock or drug-induced immunohemolysis. Immune drug–induced renal disease is rare, but glomerulonephritis, nephrotic syndrome, and acute interstitial nephritis (AIN) occasionally have been ascribed to drug hypersensitivity.

Glomerulitis is a prominent feature of experimental serum sickness but is rarely of clinical significance in drug-induced serum sickness–like reactions in humans. In all probability, it is a transient, completely reversible phenomenon that subsides entirely once the offending drug has been discontinued. Although spontaneously occurring SLE is frequently associated with glomerulonephritis, drug-induced SLE rarely manifests significant renal involvement. As a rule, cutaneous involvement is the prominent feature of drug-induced vasculitis, but occasionally glomerulonephritis may be present. Chronic glomerulonephritis was described in a patient with Munchausen syndrome who repeatedly injected herself with DPT vaccine (262). Among heroin addicts, there is a 10% incidence of chronic glomerulonephritis at autopsy. It is suggested that this may be due to

immune complexes developing as a result of an immune response to contaminants acquired in the "street" processing of the drug (263). A case of Goodpasture syndrome (pulmonary hemorrhage and progressive glomerulonephritis) was associated with D-penicillamine treatment of Wilson disease—the first case report of a drug being implicated in the etiology of this syndrome (264).

Nephrotic syndrome induced by drugs occurs primarily from immunologic processes that result in membranous glomerulonephritis. This has been more commonly associated with heavy metals (especially gold salts), captopril, heroin, NSAIDs, penicillamine, and probenecid, and less commonly with anticonvulsants (mesantoin, trimethadione, and paramethadione), sulfonylureas, lithium, ampicillin, rifampin, and methimazole. An immune complex mechanism is probably responsible for this drug-induced nephropathy (265,266). Proteinuria usually resolves when these agents are discontinued.

AIN, thought to be caused by drug hypersensitivity, has been recognized with many agents (267). More frequently reported drugs include the β-lactam antibiotics (especially methicillin), NSAIDs, rifampin, sulfonamide derivatives, captopril, allopurinol, methyldopa, anticonvulsants, cimetidine, ciprofloxacin, and PPIs. Drug-induced AIN should be suspected when acute renal insufficiency is associated with fever, skin rash, arthralgias, eosinophilia, mild proteinuria, microhematuria, and eosinophiluria beginning days to weeks after initiation of therapy. However, the classic triad of fever, rash, and eosinophilia is not so common, seen only in 10% to 30% of patients diagnosed with AIN (268). NSAID-induced AIN usually develops in elderly patients months after initiating therapy and is often associated with massive proteinuria and rapidly progressive renal failure (269). Fever and eosinophilia are usually not present. Although the pathogenesis of this drug-induced nephropathy is uncertain, a number of immunologic findings have been documented in methicillin-induced AIN (270). These include the detection of penicilloyl haptenic groups and immunoglobulin deposition along glomerular and tubular basement membranes, circulating antitubular basement membrane antibodies, a positive delayed skin test reaction to methicillin, and a positive lymphocyte transformation test to methicillin. Also, the lymphocytes infiltrating the renal interstitium are cytotoxic T cells. The prognosis is excellent following discontinuation of the drug, with full recovery expected within 12 months. After recovery, the offending drug or a chemically related one should be avoided because there have been several cases of cross-reactivity between methicillin and another β-lactam drug, or among various NSAIDs.

Lymphoid System Manifestations

Lymphadenopathy is a common feature of the serum sickness syndrome and may be present in drug-induced SLE. Lymphadenopathy associated with prolonged treatment with anticonvulsants, notably phenytoin, is a rare but well-established disorder that may mimic clinically and pathologically a malignant lymphoma (271), and is often referred to as drug-induced pseudolymphoma. Cervical lymphadenopathy is most frequent, but may be generalized; hepatomegaly and splenomegaly are uncommon. Other features may include fever, a morbilliform or erythematous skin rash, and eosinophilia (DRESS). Rarely, arthritis and jaundice may be present. The pathogenesis of this syndrome is unknown. However, phenytoin may induce immunosuppression, which then leads to lymphoreticular malignancies. The reaction usually subsides within several weeks after the drug is stopped and reappears promptly on readministration of the offending drug. However, not all patients recover after drug withdrawal, and some develop Hodgkin disease and lymphoma (272). An infectious mononucleosis–like syndrome has been described with phenytoin, aminosalicylic acid, and dapsone (273).

Cardiac Manifestations

Hypersensitivity myocarditis is rarely identified as a clinical entity. Although endomyocardial biopsy has, on occasion, suggested hypersensitivity myocarditis, reported cases are usually diagnosed at autopsy (274). Many drugs have been implicated, but the main offenders are the sulfonamides, methyldopa, penicillin, and its derivatives. Many of these drugs have also been associated with hypersensitivity vasculitis. In most cases diagnosed at autopsy, the patients died suddenly and unexpectedly while being treated for an unrelated and nonlethal illness (275).

The diagnosis should be considered when new electrocardiographic changes appear in association with unexpected tachycardia, mildly elevated cardiac enzymes, and cardiomegaly in a patient with an allergic drug reaction, usually with evidence of eosinophilia (276). Confirmation is usually obtained by a biopsy of the endomyocardium that demonstrates diffuse interstitial infiltrates rich with eosinophils.

Because cellular necrosis is less prominent than in other forms of myocarditis, permanent cardiac damage is less if the entity is recognized and the offending drug eliminated. Most patients recover in a few days to a few weeks. Aggressive treatment with corticosteroids or immunosuppressives may be necessary if myocarditis is severe and persistent. The diagnosed cases probably represent

only the tip of the iceberg, with many cases presumably self-limited and unrecognized. This reaction should not be confused with other types of chronic eosinophilic myocardiopathy, which often lead to permanent cardiac damage and impairment of function.

Neurologic Manifestations

An allergic etiology for drug-induced damage to the central and peripheral nervous system is unusual. Postvaccinal encephalomyelitis does resemble experimental encephalomyelitis in animals. A peripheral neuritis has been reported in patients receiving gold salts, colchicine, nitrofurantoin, and sulfonamides; although such reactions have not been analyzed sufficiently to implicate an immunologic mechanism, this has been suggested.

◼ EVALUATION OF PATIENTS WITH SUSPECTED DRUG HYPERSENSITIVITY

The investigation and identification of a drug responsible for a suspected allergic reaction still depends largely on circumstantial evidence and clinical skills of the physician. Absolute proof that a drug is the actual offender is usually lacking because, with few exceptions, conventional methods to diagnose allergic disorders are either unavailable or unreliable or unsafe.

Knowledge of the clinical criteria (Table 17A.3) and clinical manifestations ascribed to drug hypersensitivity is helpful in evaluation. None of these clinical manifestations are unique for drug allergy, but physicians should consider this very treatable condition along with other diagnostic possibilities.

The complexity and heterogeneity of immune responses induced by drugs, the variety of immunologic tests needed for their detection, and the fact that the relevant drug antigens are in most cases not able to be prepared *in vitro*, but rather are the result of complex metabolic interactions occurring *in vivo*, have largely prevented the development of clinically applicable *in vivo* and *in vitro* diagnostic tests. Table 17A.11 provides an overview of useful approaches available to evaluate and diagnose allergic drug reactions.

Detailed History

The most important consideration in the evaluation of patients for possible drug allergy is a suspicion by the physician that an unexplained symptom or sign may be due to a drug currently being administered. Next in importance is obtaining a complete history of *all* drugs taken currently, and within the past month or so, as

well as a history of any drug reactions in the past. It is helpful to be aware of those drugs most frequently implicated in allergic reactions (Table 17A.12).

The clinical features of the reaction may suggest drug hypersensitivity, although morphologic changes associated with drug allergy are often protean in nature and usually not agent specific. It is obviously helpful to know whether the presenting manifestations have been reported previously as features of a reaction to the drug being taken.

TABLE 17A.11 OVERVIEW OF METHODS USED TO EVALUATE PATIENTS WITH SUSPECTED DRUG HYPERSENSITIVITY

Detailed history[a]—basis for diagnosis in most cases

    Consider the possibility

    Complete history of *all* drugs taken and any prior reactions

    Compatible clinical manifestations

    Temporal eligibility[b]

In vivo **testing**—clinically indicated in some cases

    Cutaneous tests for IgE-mediated reactions[a]

    Patch tests[a]

    Incremental provocative test dosing[a]

In vitro **testing**—rarely helpful clinically

Drug-specific IgE antibodies (RAST)

Drug-specific IgG and IgM antibodies

Lymphocyte blast transformation

Others: mediator release, complement activation, immune complex detection

Withdrawal of the suspected drug—presumptive evidence if symptoms clear

Eliminate any drug not clearly indicated

Use alternate agents if possible

[a]These methods are clinically most available and useful in evaluating allergic drug reactions.

[b]There are few exceptions to this, such as ACE inhibitor angioedema, which can occur at any time, and lumiracoxib-induced liver injury, which typically occurs 100 days after starting the medication.

IgE, immunoglobulin E; IgM, immunoglobulin M; RAST, radioallergosorbent test.

TABLE 17A.12 DRUGS FREQUENTLY IMPLICATED IN ALLERGIC DRUG REACTIONS

Aspirin and nonsteroidal anti-inflammatory drugs	Radiocontrast media
β-Lactam antibiotics	Antihypertensive agents (angiotensin-converting enzyme inhibitors, methyldopa)
Sulfonamides (antibacterial, hypoglycemics, diuretics)	Antiarrhythmia drugs (procainamide, quinidine)
Antituberculous drugs (isoniazid,	Heavy metals (gold salts)

rifampicin)	
Nitrofurans	Organ extracts (insulin, other hormones)[a]
Anticonvulsants (hydantoin, carbamazepine, phenobarbital, lamotrigine)	Antisera (antitoxins, monoclonal antibodies)[a]
Anesthetic agents (muscle relaxants, thiopental)	Enzymes (L-asparaginase, streptokinase, chymopapain)[a]
Allopurinol	Vaccines (egg based)[a]
Antipsychotic tranquilizers	Latex[a,b]
Cisplatin	Abacavir

[a]Complete antigens.

[b]Not a drug *per se*, but frequently present in a medical setting.

The history should establish temporal eligibility of the suspected drug. Unless the patient has been sensitized previously to the same or a cross-reacting drug, there should be an interval between initiation of treatment and the subsequent reaction. For most medications, this interval is rarely less than 1 week, and reactions generally appear within a month or so following initiation of therapy. It is unusual for a drug taken for long periods of time to be incriminated. This information has proved especially useful in deciding which drug is the likely offender when patients are receiving multiple medications. It is helpful to construct a graph denoting times when drugs were added and discontinued, along with the time of onset of clinical manifestations. For patients previously sensitized to a drug, allergic reactions may occur within minutes or hours after institution of therapy.

In Vivo Testing

In vivo testing for drug hypersensitivity involves skin testing or cautious readministration of the suspected provocative agent, test dosing. Such an approach may be clinically indicated in selected cases.

Immediate Wheal-and-Flare Skin Tests

Prick (puncture) and intradermal cutaneous tests for IgE-mediated drug reactions may be quite helpful in some clinical situations. Tests must be performed in the absence of medications that interfere with the wheal-and-flare response, such as antihistamines and tricyclic antidepressants. Positive (histamine) and negative (diluent) control skin tests should be performed. For safety, prick tests must be negative before proceeding with intradermal tests. A wheal without surrounding erythema is clinically insignificant (277).

For high-molecular-weight agents that have multiple antigenic determinants, such as foreign antisera, hormones (e.g., insulin), enzymes, egg-containing vaccines, monoclonal antibodies, other recombinant proteins, and latex, positive immediate wheal-and-flare skin test reactions identify patients at risk for anaphylaxis. With low-molecular-weight drugs, skin testing has a role in the evaluation of IgE-mediated reactions to β-lactam antibiotics and at times has been helpful in the detection of IgE antibodies to muscle relaxants, aminoglycosides, SMX, cephalosporins, and monobactams.

There are occasional reports of immediate wheal-and-flare skin tests to other drugs implicated in immediate generalized reactions, but their significance is uncertain. However, this should not deter one from attempting such with dilute solutions of the suspected drug (278). It is theoretically possible that a drug may bind to high-molecular-weight carriers at the skin test site, thus permitting the required IgE antibody cross-linking for mast cell mediator release and the attendant wheal-and-flare response. When such testing is attempted with drugs that have not been previously validated, normal controls must also be tested to eliminate the possibility of false-positive responses. A positive skin test suggests that the patient may be at risk for an IgE-mediated reaction; however, a negative skin test reaction does not eliminate that possibility.

Patch Tests

Patch and photopatch tests are of value in cases of contact dermatitis to topically applied medicaments, even if the eruption was provoked by systemic administration of the drug. In photoallergic reactions, the patch test may become positive only after subsequent exposure to an erythemic dose of ultraviolet light (photopatch testing). The value of the patch test as a diagnostic tool in systemic drug reactions is unclear. However, some patients who have developed maculopapular or eczematous rashes after the administration of carbamazepine, practolol, and diazepam have consistently demonstrated positive patch tests to these drugs (279).

Incremental Provocative Test Dosing

Direct challenge of the patient with a test dose of the drug (provocative test dosing) remains the only absolute method to establish or exclude an etiologic relationship between most suspected drugs and the clinical manifestations produced. In certain situations, it is essential to determine whether a patient reacts to the drug, especially if there are no acceptable substitutes. Provocative testing only to satisfy the patient's curiosity or physician's academic interest is not justified. The procedure is potentially dangerous and is inadvisable without appropriate consultation and considerable experience in management of hypersensitivity phenomena. In fact, in one large series, patients were rechallenged with a drug suspected of producing a cutaneous reaction; 86% recurred, 11% of which were severe reactions (135).

The principle of incremental test dosing, also known as *graded challenge*, is to administer sufficiently small doses that would not cause a serious reaction initially, and to increase the dose by safe increments (usually 2- to 10-fold) over a matter of hours or days until a therapeutic dose is achieved (2). Generally, the initial starting dose is 1% of the therapeutic dose; it is 100- to 1,000-fold less if the previous reaction was severe. If the prior reaction was acute (e.g., anaphylaxis), the increased doses may be given at 15- to 30-minute intervals, with the entire procedure completed in 4 hours or less. When the previous reaction was delayed (e.g., morbilliform dermatitis), the interval between doses may be 24 to 48 hours and requires several weeks or longer for completion. Such slow test dosing may not be feasible in urgent situations, such as the need for TMP–SMX in AIDS patients with life-threatening *P. carinii* pneumonia. If a reaction occurs during test dosing, a decision must be made as to whether the drug should be terminated or desensitization attempted.

Provocative test dosing should not be confused with desensitization (3). With respect to test dosing, the probability of a true allergic reaction is low, but the clinician is concerned about the possibility of such a reaction. It is likely that many of these patients could have tolerated the drug without significant risk, but for safety, reassurance, and medicolegal concerns, this cautious administration has merit. Desensitization is the procedure employed to administer a drug to a patient in whom true allergy has been reasonably well established, specifically IgE-mediated, immediate hypersensitivity.

Before proceeding with drug challenges, informed consent must be obtained and the information recorded in the medical record. It is advisable to explain the risks of giving as well as withholding the drug. Appropriate specialty

consultation to underscore the need for the drug is desirable, if available. Hospitalization is usually required, and emergency equipment to treat anaphylaxis must be available. The drug challenge is performed immediately before treatment, not weeks or months in advance of therapy. Also, prophylactic treatment with antihistamines and corticosteroids before drug challenges is not recommended because these mask more mild reactions that may occur at low doses, risking a more serious reaction at higher doses. Drug rechallenges should not be considered when the previous reaction resulted in EM major (SJS), TEN, exfoliative dermatitis, and drug-induced immune cytopenias.

In Vitro Testing

Testing *in vitro* to detect drug hypersensitivity has the obvious advantage of avoiding the inherent dangers in challenging patients with the drug. Although the demonstration of the drug-specific IgE is usually considered significant, the presence of other drug-specific immunoglobulin classes or cell-mediated allergy correlates poorly with a clinical adverse reaction. Drug-specific immune responses occur more frequently than clinical allergic drug reactions.

Drug-Specific Immunoglobulin E Antibodies

The *in vitro* detection of drug-specific IgE antibodies is generally less sensitive than skin testing with the suspected agent. Further, this approach, as was true for skin testing with drugs, is hampered by the lack of information about relevant drug metabolites that are immunogenic.

A solid-phase radioimmunoassay, the radioallergosorbent test (RAST), has been validated mainly for the detection of IgE antibodies to the major (penicilloyl) determinant of penicillin and correlates reasonably well with skin tests using penicilloyl–polylysine. A RAST for penicillin minor determinant sensitivity remains elusive. In addition to penicillin, specific IgE antibodies have been detected in the sera of patients who sustained generalized immediate reactions to other β-lactam antibiotics, SMX, TMP, sodium aurothiomalate, muscle relaxants, insulin, chymopapain, and latex (280). If positive, these tests may be helpful in identifying patients at risk; if negative, they do not exclude the possibility.

Drug-Specific Immunoglobulin G and Immunoglobulin M Antibodies

With the exception of drug-induced immune cytopenias, there is often little correlation between the presence of drug-specific IgG and IgM antibodies and other drug-induced immunopathologic reactions. It has been reported that the

presence of IgG antibodies to protamine in diabetic patients treated with neutral protamine hagedorn (NPH) insulin increased the risk of immediate generalized reactions to protamine sulfate (281).

Drug-induced immune cytopenias afford an opportunity to test affected cells *in vitro*. Such testing should be performed as soon as the suspicion arises because the antibodies may disappear rapidly after withdrawal of the drug. For drug-induced immune hemolysis, a positive Coombs test is a useful screening procedure and may be followed by tests for drug-specific antibodies if available. Antiplatelet antibodies are best detected by the complement fixation test and the liberation of platelet factor 3. *In vitro* tests for drug-induced immune agranulocytosis are often disappointing because leukoagglutinins disappear very rapidly and are occasionally present in neutropenic conditions where no drug is involved.

Lymphocyte Blast Transformation

T-lymphocyte–mediated reactions (delayed hypersensitivity) have been suspected in some patients with drug allergy. Lymphocyte blastogenesis (lymphocyte transformation test) has been suggested as an *in vitro* diagnostic test for such reactions. This test detects *in vitro* proliferation of the patient's lymphocytes in response to drugs (282). A variation on this assay measures the T-lymphocyte–cytokine production rather than proliferation (283). There is disagreement over the value of this procedure in the diagnosis of drug allergy. However, because there appears to be a high incidence of false-negative and false-positive results, these tests have little clinical relevance (284).

Other Tests

The measurement of mast cell mediator release during drug-induced anaphylaxis or anaphylactoid reactions appears to be promising. Tryptase is a neutral protease that is specifically released by mast cells and remains in the serum for at least 3 hours after the reaction (285). It is a relatively stable protein that may be measured in stored serum samples. After a reaction, several serum samples should be obtained during the first 8 to 12 hours. A positive test for tryptase is helpful, but a negative result does not rule out an immediate generalized reaction.

Complement activation and immune complex assays are other tests that may be helpful in the evaluation of drug-induced serum sickness–like reactions. Immunoglobulins and complement have been demonstrated in drug-induced immunologic nephritis, but it is often unclear whether the drugs themselves are

present in the immune complexes (286).

Withdrawal of the Suspected Drug

With a reasonable history suggesting drug allergy and the usual lack of objective tests to support the diagnosis, further clinical evaluation involves withdrawal of the suspected drugs, followed by prompt resolution of the reaction, often within a few days or weeks. This is presumptive evidence of drug allergy and usually suffices for most clinical purposes.

Typically, patients are taking several medications. Those drugs that are not clearly indicated should be stopped. For drugs that are necessary, an attempt should be made to switch to alternative, non–cross-reacting agents. After the reaction subsides, resumption of treatment with the drug least likely to have caused the problem may be considered, if that drug is sufficiently important. However, there may be risk of anaphylaxis if the causative agent is resumed after interruption of therapy. Therefore, this should be considered before any therapy is discontinued.

There may be circumstances in which it would be detrimental to discontinue a drug when there is no suitable alternative available. The physician must then consider whether the drug reaction or the disease poses a greater risk. If the reaction is mild and does not appear to be progressive, it may be desirable to treat the reaction symptomatically and continue therapy. For example, in patients being treated with a β-lactam antibiotic, the appearance of urticaria may be managed with antihistamines or low-dose prednisone. Anaphylaxis has not developed in this setting (4). However, interruption of therapy for 24 to 48 hours may result in anaphylaxis if treatment is resumed.

◼ PATIENT MANAGEMENT CONSIDERATIONS: TREATMENT, PREVENTION, AND REINTRODUCTION OF DRUGS

Treatment of Allergic Drug Reactions

General Principles

Withdrawal of the suspected drug is the most helpful diagnostic maneuver. At the same time, it is also the treatment of choice. Frequently, no additional treatment is necessary, and the clinical manifestations often subside within a few days or weeks without significant morbidity. If the reaction is not severe, and more than one drug is a candidate, withdrawal of one drug at a time may clarify

the situation.

There may be clinical situations in which continued use of the suspected drug is essential. Here, the risk of continuing the drug may be less than the risk of not treating the underlying disease, particularly if no suitable alternative drug is available. Careful observation of the patient to detect any progression of the reaction, for example, a morbilliform rash becoming exfoliative in nature, and use of antihistamines and prednisone, may permit completion of the recommended course of therapy. Some physicians may elect to treat through milder reactions, but this is not without risk and should be supervised by physicians with experience. There are also situations in which a manifestation, often cutaneous, appears during the treatment but results from the basic illness and not the drug.

Symptomatic Treatment

Pharmacologic management of allergic drug reactions is aimed at alleviating the manifestations until the reaction subsides. For mild reactions, therapy is usually not required. Treatment of more severe reactions depends on the nature of the skin eruption and the degree of systemic involvement.

Drug-induced anaphylaxis and anaphylactoid reactions, urticaria, angioedema, and asthma are treated in a manner described in other chapters in this book dealing with these entities.

For most patients with drug-induced serum sickness or serum sickness–like reactions, treatment with antihistamines and NSAIDs is all that is required. More severe manifestations require treatment with prednisone, 40 to 60 mg daily to start, with tapering over 7 to 10 days. Occasionally, plasmapheresis has been used to remove immune reactants.

The treatment of SJS includes high-dose corticosteroid therapy (191,192). For milder ambulatory cases, a minimum of 80 mg of prednisone daily is advised. Severe cases require hospitalization and administration of 60 mg of IV methylprednisolone every 4 to 6 hours until the lesions show improvement. Corticosteroids should then be tapered slowly over 2 to 3 weeks because tapering prematurely may result in recurrence of the lesions (191,192). For TEN, corticosteroids will not suppress the severe cutaneous involvement, and such patients are most efficiently managed in a burn unit. IVIG in doses totaling 2 g/kg appear to decrease mortality and time to recovery (287,288). Sepsis is the principal cause of death in affected patients.

For other drug-induced immune reactions, such as drug fever, DRESS, DIL, and vasculitis, and for reactions involving circulating blood elements and solid organs, corticosteroids accelerate resolution of these adverse drug effects and may prevent irreparable damage or even fatalities.

Prevention of Allergic Drug Reactions

Drug Considerations

The best way to reduce the incidence of allergic drug reactions is to prescribe only those medications that are clinically essential. Of 30 penicillin anaphylactic deaths, only 12 patients had clear indication for penicillin administration (289). A survey of patients with allopurinol hypersensitivity syndrome reported that the drug was given correctly in only 14 of 72 cases, and there were 17 deaths (290). Also, using many drugs when fewer would be adequate will complicate identification of the offending drug should a reaction occur. The use of drugs in Scotland is about half that in the United States, and, not surprisingly, the incidence of ADRs is considerably less (291). Interruption of therapy increases the risk of allergy and should be avoided. The physician must be well informed about adverse reactions to drugs being prescribed.

Patient Considerations

The patient or a responsible person must be questioned carefully about a previous reaction to any drug about to be prescribed, and information should also be obtained about all other drugs previously taken. If available, a review of the patient's medical records may uncover essential information about prior drug reactions. Unfortunately, studies have demonstrated that many health care professionals do not obtain adequate drug histories and document them in the medical record. This incomplete documentation did not appear to be related to the patients' inability to provide accurate information (292). Failure to follow these simple procedures may not only harm patients but also result in significant malpractice claims (293).

Although overdiagnosis may be a problem, it is generally advisable to accept what the patient believes or has been advised without the need for further documentation. Fortunately, there are alternative, non–cross-reacting agents available for most clinical situations. However, there may be situations in which one might choose an alternative drug when there is a chance of cross-reactivity; for example, selecting a cephalosporin in a penicillin-allergic patient to avoid using a more toxic drug, such as an aminoglycoside. In this situation, the patient should be skin tested for penicillin, and if test results are positive, the cross-

reacting drug should be administered with a desensitization protocol in a monitored setting. Although cross-reactivity risk may be low, reactions may be severe (294).

Available Screening Tests

For acute generalized reactions, immediate wheal-and-flare skin tests are sensitive indicators for the detection of specific IgE antibodies to proteins. Skin testing is mandatory before administration of foreign antisera to reduce the likelihood of anaphylaxis.

Immediate wheal-and-flare skin tests with nonprotein, haptenic drugs have been validated for penicillin, thus permitting identification of patients with a history of penicillin allergy who are no longer at significant risk for readministration of this agent. For other haptenic drugs, such testing may detect drug-specific IgE antibodies when positive at concentrations that do not result in false-positive reactions in normal subjects. However, negative skin tests do not eliminate the possibility of clinically significant allergic sensitivity. None of the available *in vitro* tests for assessment of drug hypersensitivity qualify as screening procedures. Obviously, the simplicity, rapidity, and sensitivity of skin testing make it a logical choice for clinical purposes.

Methods of Drug Administration

Although there is some disagreement (47), the oral route of drug administration is perhaps preferable to parenteral administration because allergic reactions are less frequent and generally less severe. Clearly, topical use of drugs carries the highest risk of sensitization. For drugs given parenterally, an extremity should be used, if possible, to permit placement of a tourniquet if a reaction occurs. Close observation is required because one study noted that most severe reactions involving IV medications resulted in the patient arresting in less than 5 minutes (81). In addition, patients should be kept under observation for 30 minutes after parenteral administration of a drug. If the patient is likely to develop a vasovagal reaction after an injection, the drug may be given while the patient is sitting or in a recumbent position.

Prolonged exposure to a drug increases the likelihood of sensitization. The frequency of drug usage increases the chance of eliciting an allergic response. The risk for a reaction appears to be greater during the first few months after a preceding course of treatment.

Follow-up after an Allergic Drug Reaction

The responsibility to a patient who has sustained an ADR does not end with discontinuation of the agent and subsequent management of the reaction. The patient or responsible people must be informed of the reaction and advised how to avoid future exposure to the suspected agent and any agents that may cross-react with the offending drug. It is also helpful to mention alternative drugs that may be useful in the future. The patient should be educated about the importance of alerting other treating physicians about drugs being taken and any past ADRs. A retrospective cohort study by Apter et al. found that represcription of penicillin to patients with previous reactions is more common than anticipated (295).

All medical records must prominently display this information in a conspicuous location. The patient could carry a card (296) or wear an identification tag or bracelet (MedicAlert Emblems, Turlock, CA) noting those drugs to be avoided if possible.

Reintroduction of Drugs to Patients with a History of a Previous Reaction

If the patient has had a previous documented or suspected allergic reaction to a medication, and now requires its use again, the physician must consider the risks and benefits of readministration of that drug. Cautious reintroduction of that medication may be considered when there are no acceptable alternatives available or when the alternative drug produces unacceptable side effects, is clearly less effective, or requires limited use because of resistance (e.g., increased vancomycin use leading to vancomycin-resistant enterococci). Physicians specializing in hypersensitivity reactions have developed a number of management strategies that permit many patients to receive appropriate drug therapy safely or to undergo an essential diagnostic evaluation (3). These procedures include premedication protocols, desensitization schedules, and test-dosing regimens (Fig. 17A.1).

Because these approaches constitute reintroduction of an agent previously implicated in an allergic reaction and thereby carry a risk of a potentially severe, even fatal, reaction, consultation should be obtained from the appropriate specialist (e.g., infectious disease specialist) to underscore the essentiality of the drug and its subsequent readministration. The medical record must contain this information in writing as well as informed consent from the patient or other responsible individuals. Informed consent must include a statement of potential risks of the procedure as well as risks that may develop without the treatment.

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Further, the medical setting should provide arrangements for emergency treatment of an acute reaction. Ideally, patients should not be receiving β-blocking drugs (even timolol ophthalmic solution), and asthma, if present, must be under optimal control.

Desensitization is best performed by an experienced allergist. Medical supervision is required throughout the procedure, which should be done in an intensive care unit setting. Patients are often frightened by the risks of these procedures, and symptoms of anxiety may make evaluation difficult. The physicians must quickly decide whether to continue or abandon the procedure. In general, the presence of symptoms without objective findings suggests that the reaction may be psychological in nature, and treatment should be continued.
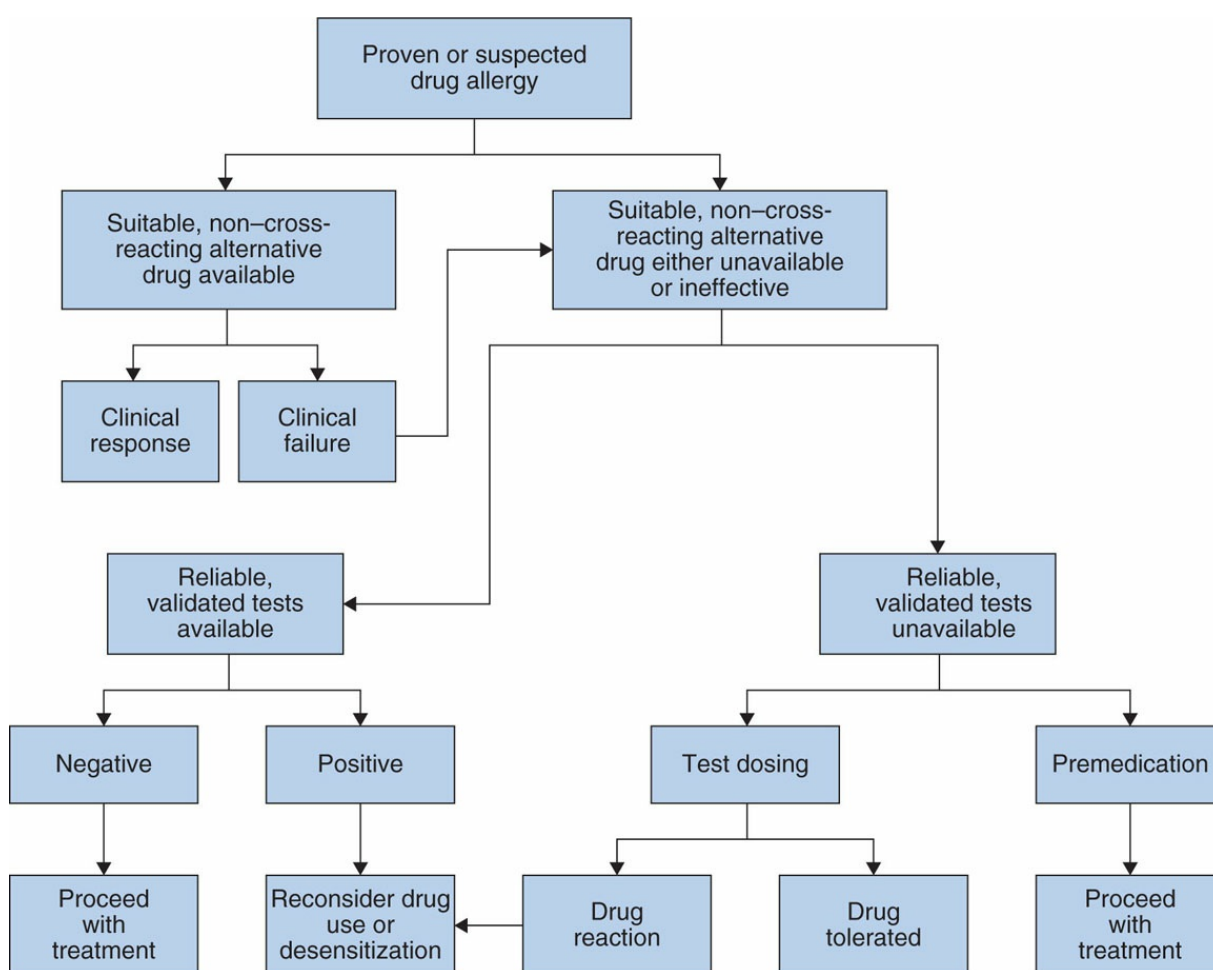
■ **FIGURE 17A.1** An algorithm providing guidelines for the reintroduction of drugs to patients with a history of a previous drug reaction.

Premedication

The prophylactic administration of antihistamines and corticosteroids alone or in combination with β-adrenergic agonists has been effective in reducing the incidence and severity of anaphylactoid reactions to RCM among patients with a

previous history of such reactions. A similar approach has been used to minimize the likelihood of an anaphylactoid reaction following the administration of IV muscle relaxants, opiates, iron dextran, and protamine (3,297) as well as many chemotherapeutic agents (98). It appears likely that drug-induced anaphylactoid events and possibly other situations in which reaction mechanisms are unknown may be amenable to medication by such pretreatment regimens. Such premedication protocols are ineffective in blocking drug-induced IgE-mediated anaphylaxis. For this reason, prophylactic therapy before desensitization or test dosing to drugs is not recommended (3). Pretreatment may mask a mild reaction occurring at low doses of the drug and risk a more serious reaction at higher doses, which may be more difficult to manage.

Desensitization

Desensitization involves the conversion from a highly sensitive state to one in which the drug is now tolerated. This is reserved for patients with a history of an IgE-mediated immediate generalized reaction to a drug, confirmed by skin testing if available (e.g., PCN skin testing). Ideally, the term *desensitization* should be reserved for those reactions that have an established immunologic basis, and the cautious reaction with, and elimination of, IgE antibody as the goal. This produces a temporary, nonresponsive state lasting as long as therapy is uninterrupted. If therapy is interrupted, anaphylactic sensitivity may return within 48 hours of stopping the drug. Thus, continuation of an agent, such as insulin, after desensitization, is appropriate.

Acute desensitization with agents causing IgE-mediated reactions involves the administration of gradually increasing doses of the drug over several hours (e.g., penicillin) or days (e.g., insulin), often starting with amounts as low as 1/1,000,000 to 1/100,000 of the therapeutic dose. The initial desensitizing dose may be based on the results of skin testing or test dosing. This process is accomplished with the agent that is required for treatment. Both oral and parenteral routes have been used for desensitization. The choice of route depends on the clinical condition, the drug being given, and the experience or preference of the attending physician. The IV dose is then doubled every 15 minutes while carefully monitoring the patient. Using such a protocol, anaphylaxis has not been reported during desensitization, or with continued uninterrupted treatment using a reduced dose. However, mild systemic reactions, notably urticaria and pruritus, occur in about one-third of patients during desensitization. These mild reactions may subside spontaneously; they usually respond to symptomatic treatment or dosage adjustment or both.

This approach has been used successfully to permit treatment with β-lactam antibiotics among patients with a history of penicillin allergy and positive tests for the major and minor haptenic determinants of penicillin, among diabetic patients with systemic insulin allergy, and among patients with positive skin tests for heterologous antisera. Desensitization to these IgE-mediated reactions renders mast cells specifically unresponsive to only the drug antigen used for desensitization. In many patients, successful desensitization is accompanied by a marked decrease or disappearance of the cutaneous wheal-and-flare response. Similar changes in skin test responses have been reported after successful desensitization to aminoglycosides and vancomycin (298,299). This is temporary; within 48 hours of discontinuing the drug, the skin tests are again positive. The patient is then at risk for anaphylaxis if the drug is resumed.

Although desensitization, as described, is limited to IgE-mediated reactions, the term has also been used in its broadest sense to describe a state of unresponsiveness to a drug that is accomplished by repeated and increasing exposure to that agent. This may include delayed, not IgE-mediated, reactions. This is also applied to patients who have had undeniable reactions to these drugs in the past. However, this does not involve elimination of available IgE antibodies through "controlled anaphylaxis" and may best be described as cautious readministration of the offending agent. Protocols have been described for the cautious administration of aspirin, sulfonamides (especially TMP–SMX and sulfasalazine), allopurinol (300), and others (3). Unlike desensitization to IgE-mediated reactions, these protocols are often more cumbersome and may require days or even weeks to complete. It should be emphasized that desensitization is a potentially hazardous procedure best left to physicians experienced in managing hypersensitivity reactions.

Test Dosing

In situations in which a drug is needed and the history of a previous reaction to that agent is vague, the possibility of true allergy is low, or the drug itself is an unlikely cause of such a reaction, test dosing or graded challenge is a method used to clarify the situation and safely determine whether it may be administered. A common example is a patient who has been advised to avoid all "caines," and now requires the use of a local anesthetic agent. True systemic allergy to local anesthetics is very rare. Test dosing provides reassurance to the patient, physician, or dentist that this agent can be given safely.

The principle of test dosing is to select a dose of the drug below that which would potentially cause a serious reaction and then proceed with relatively large

incremental increases to full therapeutic doses. Using this technique, one can determine whether a reaction occurs before proceeding to the next dose. If a reaction occurs, it can be easily treated. If the drug is necessary, a desensitization protocol may then be considered.

The starting dose, incremental increase, and interval between challenges depend on the drug and the urgency of reaching therapeutic doses. For oral drugs, a usual starting dose is 0.1 or 1.0 mg and then proceeds to 10, 50, 100, and 200 mg. For parenteral drugs, the initial dose is less, for example, 0.01 or 0.001 mg. If the suspected reaction was immediate, a 30-minute interval between doses is appropriate, and the procedure is usually completed in 3 to 5 hours or less. For late-onset reactions, such as dermatitis, the dosing interval may be as long as 24 to 48 hours, with the procedure requiring 1 to 2 weeks or longer to complete. Although there is always the possibility of a severe reaction, the risk of test dosing appears to be very low (3).

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PART B

Allergic Reactions to Individual Drugs: Low-Molecular-Weight

PAUL A. GREENBERGER

The approach described in this part of the chapter has been used successfully to permit treatment with both low- and high-molecular-weight drugs: β-lactam antibiotics among patients with a history of penicillin allergy and positive tests for the major and/or minor haptenic determinants of penicillin; systemic insulin allergy among diabetic patients; and heterologous antisera among patients with positive skin tests. Desensitization (induction of drug tolerance or drug provocation testing) to these immunoglobulin E (IgE)-mediated reactions renders mast cells specifically unresponsive to only the drug antigen used for desensitization. In many patients, successful desensitization is accompanied by a marked decrease or transient disappearance of the cutaneous wheal-and-flare response. Similar changes in skin test responses have been reported following successful desensitization to vancomycin (1), aminoglycosides (2), and carboplatin (3).

The term *desensitization* has been used in its broadest sense to describe a state of unresponsiveness to a drug that is accomplished by repeated and increasing exposure to that agent (4–8). Similar to acute desensitization for IgE-mediated reactions, these patients have had undeniable reactions to these drugs in the past. During desensitization, the positive immediate skin test reactions temporarily convert to negative during the administration of the incriminated medication. The broader term *induction of drug tolerance* has been recommended instead of

desensitization in the 2010 Drug Allergy practice parameters in the United States so that it applies to immunologic-IgE mediated, immunologic-non-IgE mediated, pharmacologic, and processes of unknown mechanism (4). An international consensus in 2014 suggested using *drug provocation test(s)* (5) also known as *test dosing* or *graded drug challenge* (6). For billing purposes, the only term with a current procedural terminology code is desensitization. Protocols have been described for the cautious administration of aspirin (4,9–11), sulfonamides (especially trimethoprim–sulfamethoxazole [TMP-SMX] and sulfasalazine) (4,12–15), allopurinol (4,16,17), tobramycin (18,19), and antiviral and antiretroviral medications (13,20–23). Unlike true desensitization to IgE-mediated reactions, these protocols are often more cumbersome and may require hours or days to complete (13). Finally, one should be reminded that *induction of drug tolerance* (4) or *drug provocation tests* (6) and true desensitizations are potentially hazardous procedures best left to physicians experienced in managing hypersensitivity reactions (4–6). Highly trained nurses or other health care professionals can participate in the monitoring of patients during challenges.

INDUCTION OF DRUG TOLERANCE/DRUG PROVOCATION TESTS

In situations in which a drug is needed and the history of a previous reaction to that agent is vague, and the possibility of true allergy is low, or the drug itself is an unlikely cause of such a reaction, test-dosing or graded drug challenge is a method used to clarify the situation and safely determine whether it may be administered (6,13). A common example is a patient who has been advised to avoid all "caines," and now requires the use of a local anesthetic agent. True systemic allergy to local anesthetics essentially is unheard of. Provocation drug tests providers should reassure the patient, physician, or dentist that this agent can be given safely. Alternatively, when the drug provocation testing results in symptoms such as instantaneous throat closure without objective findings, it helps to confirm the level of anxiety involved without demonstrating true allergy.

The principle of drug provocation testing (graded drug challenges) is to select a dose of the drug below that which would potentially cause a serious reaction, and then proceed with increasingly larger incremental doses to full therapeutic doses. Using this technique, one can determine whether a reaction has occurred before proceeding to the next dose. If a reaction occurs, it can be easily treated. If the drug is necessary, a desensitization protocol then may be performed. In this setting, *controlled anaphylaxis* can be carried out.

The starting dose, incremental increase, and interval between challenges depend on the drug and the urgency of reaching therapeutic doses (13). For oral drugs, a usual starting dose is 0.1 or 1.0 mg and then proceeds to 10, 50, 100, and 200 mg (13). For parenteral drugs, the initial dose is less, for example, 0.01 or 0.001 mg. When the suspected reaction was immediate, a 20- to 30-minute interval between doses is appropriate, and the procedure is usually completed in 3 to 5 hours or less. For late-onset reactions, such as a nonblistering or nonexfoliating dermatitis, the dosing interval may be as long as 24 to 48 hours, with the same protocols requiring 1 to 2 weeks or longer. Although there is always the possibility of a severe anaphylactic reaction, the risk of provocation test dosing appears to be very low. Nevertheless, incremental provocation testing of patients with a history of a bullous reaction to a medication or a serum sickness reaction (severe urticaria and arthralgia) (24) would have to be considered in rare patients (13,21).

SPECIAL CONSIDERATIONS FOR PROVEN OR SUSPECTED ALLERGIC REACTIONS TO INDIVIDUAL DRUGS

In this section, specific recommendations are reviewed because they pertain to important drugs commonly used in clinical practice. For each agent, relevant background information is provided. Table 17B.1 summarizes useful strategies for administering agents, once the indication has been verified.

Penicillins and Other $_a$-Lactam Antibiotics

Background

β-Lactam antibiotic hypersensitivity deserves special consideration because of its medical importance. Penicillin has been studied extensively and has become a prototype for the study of allergic drug reactions. As many as 10% of hospitalized patients report a history of penicillin allergy. In one study of 1,893 consecutive adult patients who had an order written for an antimicrobial agent while hospitalized, 470 patients (25%) reported an allergy to at least one drug (25). In all, 295 patients (15.6%) listed penicillin (25). A manual review of the charts revealed that just 32% of records specified the details of the allergic reaction. Similarly, from 453 inpatients on a medical service, 160 patients has antibiotic allergy listed, including 55 for simple penicillins, 8 for aminopenicillins, and 9 for antistaphylococcal penicillins (26). These data translate into 72 of 453 (15.9%) of medical inpatients having a penicillin allergy

label (26). Some patients have been labeled falsely as penicillin allergic and are denied this useful, remarkably nontoxic agent. The reasons for this discrepancy are either a previously incorrect diagnosis or the frequently evanescent nature of penicillin allergy. Following an acute allergic reaction, there is a time-dependent decline in the rate of positive skin tests to penicillin. In the first year, 90% to 100% retain sensitivity after a convincing allergic reaction, but that percentage drops to about 30% at 10 years (27). It may be even lower in terms of cross-sectional studies of varying time periods. For example, if confirmed by skin testing with major and minor determinants, current penicillin allergy is present in only 18% of subjects who claim to have penicillin allergy (28). This finding means that about one in five patients with any history of penicillin allergy is currently allergic to penicillin. Some patients, however, maintain the penicillin-specific IgE antibody for 30 to 40 years. It is, therefore, highly desirable to predict which patients are at risk for a penicillin reaction. It is important to recognize that penicillin-allergic patients, who have current penicillin sensitization by skin testing, may not have an "impressive" history of anaphylactic shock, urticaria, angioedema, acute wheezing, and so on. In a literature review of 1,063 patients who tested positive on penicillin skin testing, 347 (33%) had vague histories of penicillin allergy (29). These patients may well have had their perceived level of risk from penicillin minimized.

TABLE 17B.1 EXAMPLES OF USEFUL EVALUATION TECHNIQUES AND MANAGEMENT STRATEGIES FOR SELECTED DRUGS AND AGENTS

DRUGS OR AGENTS	SKIN TESTS OF VALUE	PREMEDICATION USEFUL	TEST DOSING INDICATED	DESENSITIZATION IF ESSENTIAL	ADDITIONAL COMMENTS
Immediate Generalized Reactions (IgE-Mediated)					
β-Lactam antibiotics	√		See comments	√	Test the dose in the absence of penicillin.
					Use MDM or validated cephalosporin skin tests.

Insulin	√		√	Use least reactive insulin by skin test for desensitization
Immune sera	√		√	Is risky in atopic patients allergic to horse dander
Egg-containing vaccines	√		√	May be unnecessary for MMR vaccine.
Tetanus toxoid	√		√	If serum antitoxin level adequate, desensitization not required.
Latex	See comments			No standardized skin test is available.
				Avoidance is only effective treatment.
Protamine		See comments		There are no studies to validate premedication
Streptokinase	√			Substitute urokinase or tissue plasminogen activator.

Chymopapain√				Consider laminectomy

Immediate Generalized Reactions (IgE-Independent)

Aspirin and nonsteroidal anti-inflammatory drugs		√	See comments	Term *desensitizatio* used, althoug reaction is no IgE mediated
Contrast media	√			Also useful f nonvascular studies. Low osmolality media is a better choice
Opioid analgesics		√		Pentazocaine or fentanyl is less active histamine releasers.
Cancer chemotherapy	√			Slow infusio and premedicatio have been useful.

Allergy Presumed Mechanism Unclear

Sulfonamides		√	See comments	Term *desensitizatio* often used, b reaction is usually IgE independent.
Local		√		True systemi

anesthetics		reactions are rare.
		Reassurance primary goal
Anticonvulsants	√	A potentially dangerous procedure.
Other rarely incriminated drugs or agents	√	Seek consultation with experienced allergist.

MDM, minor determinant mixture; MMR, measles, mumps, rubella; IgE, immunoglobin E.

Adapted from Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. *Allergy*. 2014;69:420–437.

The overall prevalence of β-lactam allergy is estimated to range from as high as 2% per course of treatment (30) to 1.1% to 1.5% (31) and as low as 0.05% (32). The incidence of anaphylaxis has been reported to be from 1:5,000 to 1:10,000 (4) to as low as about 1:100,000 (32). For historic comparison from the 1960s, penicillin-induced anaphylaxis was reported in about 0.01% to 0.05% (1 per 5,000 to 10,000) of patient treatment courses, with a fatal outcome in 0.0015% to 0.002% (1 death per 50,000 to 100,000 treatment courses) (33). The most frequent manifestations of penicillin allergy are cutaneous, notably morbilliform, and urticarial eruptions; the most serious is anaphylaxis.

An atopic background (allergic rhinitis, asthma, and atopic dermatitis) does not predispose an individual to the development of penicillin hypersensitivity, but once sensitized, such individuals are at increased risk for severe or fatal anaphylactic reactions (34). Anaphylaxis occurring in patients with asthma may result in acute severe respiratory failure. However, from a review of patients evaluated in an academic allergy-immunology clinic, 33% of patients with chronic urticaria self-reported allergy to penicillin compared with 12.4% of clinic patients without chronic urticaria (35). Lastly, atopic patients with *Penicillium* species "mold" allergy can receive penicillin unless specifically allergic to penicillin.

Patients with a history of prior penicillin reaction have a four- to sixfold increased risk for subsequent reactions to β-lactam antibiotics (36), but not necessarily as high to carbapenems (e.g., imipenem and meropenem) (37,38). Among penicillin-allergic individuals who are skin test positive, the unmodified (regular infusion of the therapeutic dose) administration of β-lactam antibiotics causes acute reactions in about two-thirds of patients (39). If administered incrementally, by induction of drug tolerance (desensitization), the incidence of acute reactions is very much lower (4,6). Induction of drug tolerance (drug provocation testing) with imipenem and meropenem for patients with a history of penicillin allergy and positive immediate skin tests to penicillin or a determinant can be carried out safely when the skin tests to imipenem are nonreactive, and the first dose of the antibiotic is 0.01 of the target dosage (37,38).

Although this discussion focuses primarily on the evaluation of and strategies to deal with IgE-mediated reactions, this group of agents has also been associated with other adverse, IgE-independent immunologic events that are briefly noted here and have been extensively reviewed elsewhere (4,5). *Immediate reactions* occur within the first hour following administration of the β-lactam drug, are IgE mediated, and may present a serious threat to life. *Accelerated reactions* develop 1 to 72 hours after drug administration, are IgE mediated, usually present as urticaria and angioedema, and are rarely life endangering. *Delayed or late reactions* occur after 3 days, are IgE independent, and usually present as benign morbilliform skin eruptions. Exfoliative dermatitis and Stevens–Johnson syndrome may occur. Late reactions include serum sickness–like reactions (24) and drug fever (40–42). Unusual late reactions are immune cytopenias, acute interstitial nephritis, pulmonary infiltrates with eosinophilia, hypersensitivity vasculitis, and drug reaction with eosinophilia and systemic symptoms (DRESSs).

In general, the previously described adverse events are common to all β-lactam antibiotics, such as the natural penicillins (penicillin G and penicillin V), the penicillinase-resistant penicillins (methicillin, nafcillin, oxacillin, and dicloxacillin), the aminopenicillins (ampicillin, amoxicillin, and bicampicillin), and the extended spectrum penicillins (carbenicillin, ticarcillin, mezlocillin, azlocillin, and piperacillin). Hypersensitivity reactions are less with the cephalosporins (4,5,31,32,36,43–47) and carbapenems (37,38). Note that this statement is based on group mean statistics; the individual patient, who is destined to experience anaphylaxis from the antibiotic administration, is a "direct hit." The data for carbapenems included incremental challenges, such as

beginning with 1/100 and then 1/10 of the target dose for imipenem (37).

Individual β-lactam antibiotics have been associated more commonly with certain types of reactions. For instance, ampicillin and amoxicillin therapy is associated with a higher incidence (about 10%) of nonpruritic maculopapular rash than are other penicillins (about 2%) (48). The rash usually appears after at least 1 week of therapy, initially develops on the knees and elbows, and then spreads symmetrically to cover the entire body (49). If the patient has infectious mononucleosis or Epstein–Barr virus infection, the incidence approaches 90%. The incidence of this cutaneous reaction is increased in patients with HIV/AIDS and cytomegalovirus infection, chronic lymphatic leukemia, non-Hodgkin lymphoma, systemic lupus erythematosus, and hyperuricemia (48,49). This eruption does not appear to be allergic in nature, but if there is an urticarial component, it may represent true IgE-mediated penicillin allergy, and rechallenge could result in a severe immediate generalized allergic reaction.

Cephalosporins produce reactions similar to those described for penicillins. The more common reactions include maculopapular or morbilliform skin eruption, drug fever, and a positive Coombs test (clinical hemolysis is unusual). Less common reactions are urticaria, serum sickness–like reactions (especially with cefaclor in children) (50–54), and anaphylaxis (54–59). Drug-induced cytopenias and acute interstitial nephritis are rare. Compared with the first-generation cephalosporins (e.g., cephalothin, cefazolin, cephalexin,[1] cefadroxil,[*] cefaclor[*]) and second-generation cephalosporins (e.g., cefamandole, cefuroxime, cefuroxime axetil[*]), the third-generation cephalosporins (e.g., cefotaxime, ceftizoxime, ceftriaxone, ceftazidime, cefixime[*]) have a lower incidence of immediate, presumably IgE-mediated, generalized allergic reactions (44). Unexpectedly, there were a surprising number of non–IgE-mediated adverse events from a newer (fifth-generation) cephalosporin, ceftaroline (60,61).

Some degree of cross-reactivity (or independent sensitivity to non–β-lactam ring moieties) among the different classes of β-lactam antibiotics is well established (59). Because the semisynthetic penicillins contain the same 6-aminopenicillanic acid nucleus as natural penicillin G, it is not surprising that cross-allergenicity among these agents exists, albeit to various degrees. Individuals have been identified who have reacted to ampicillin and amoxicillin but not to penicillin (62–64). It is presumed that this is related to hypersensitivity to the side chains that differentiate the antibiotic from the parent compound. The incidence and clinical significance of these side-chain–specific reactions remains unknown. However, at this time, if a patient reports a history of penicillin

allergy, it is prudent to assume that the individual is allergic to all penicillins (4,5,13). Because 9% to 25% of patients receiving antibiotics report a penicillin allergy (25,31,65), the impact of penicillin allergy remains significant.

Cephalosporins share a common β-lactam ring with penicillin but have a six-membered dihydrothiazine ring instead of the five-membered thiazolidine ring of the penicillin molecule. Shortly after the introduction of the cephalosporins into clinical use, allergic reactions, including anaphylaxis, were reported, and the question of cross-reactivity between cephalosporins and penicillins was raised. Data suggest that the extent is not that high (43–47,66). Significant *in vitro* and *in vivo* cross-reactivity with penicillin has been reported with first-generation cephalosporins (5% to 16.5%) (66,67). Currently, because the prevalence of allergy to penicillin has declined, clinically relevant cross-reactivity between penicillin and the cephalosporins (especially second and third generation) is closer to 1% to 3% (47,68). A literature review of patients with a history of penicillin allergy, who were challenged with cephalosporins, revealed allergic reactions in 8.1% of patients with positive skin tests to penicillin determinants compared with 1.9% among those with negative penicillin skin tests (69). A provocative review suggested that penicillin-allergic patients, who are identified by either history or positive penicillin skin tests, are not at increased risk compared with the general population, and they may be safely treated with cephalosporin antibiotics (45). However, cautious administration of cephalosporins to penicillin-allergic patients is advisable (preferably after skin testing), especially when the history is that of acute urticaria, pruritic rash, acute dyspnea, light headedness, or other anaphylactic reaction (4,5,13). Regrettably, in a report of six penicillin-allergic patients, three experienced fatal anaphylactic reactions from the first dose of a cephalosporin (57).

Primary cephalosporin allergy, including anaphylaxis, has occasionally been reported in both penicillin-allergic and penicillin-nonallergic patients and may be fatal (57). Most investigators have studied tolerance to the cephalosporins in penicillin-allergic patients, but little information is available regarding tolerance to other β-lactam antibiotics in patients with primary cephalosporin allergy. Such studies are limited by the lack of reliable cephalosporin determinants for skin testing. It appears that antibodies directed against unique side chains rather than against the common ring structure are more important in the immune response to cephalosporins (44,66,67,70). This would explain the low cross-reactivity among different cephalosporins, which share the same nucleus but have different side chains (44,47,70). Also, it may help to explain the low cross-reactivity between cephalosporins and penicillins, which share the same β-lactam ring in the

nucleus but have different side chains. Until skin test reagents for cephalosporins are available, it is best to avoid the use of β-lactam antibiotics in cephalosporin-allergic patients; if essential, cautious graded drug provocation testing is advisable. Although skin testing with the parent cephalosporin has not been used widely, reports of skin testing with the parent cephalosporin (2 mg/mL prick test, then 0.02 mL, intradermal) describe high negative predictive value (71).

The carbapenems (imipenem, meropenem, and ertapenem), monobactams (aztreonam), and carbacephems (loracarbef) are three classes of antibiotics that possess β-lactam ring structures. There is significant *in vitro* cross-reactivity between penicillin and imipenem and meropenem based on structure and using the specific determinants of impenem, for example (72). Graded challenges were not carried out, but 47% of penicillin-allergic subjects had positive skin test reactions to imipenem determinants (72). Immediate skin reactivity to imipenem (1 mg/mL) by prick test was demonstrated in a patient who experienced shock and cardiac arrest from imipenem (73). Nevertheless, there is much less actual, clinical cross-reactivity than anticipated between penicillin and the carbapenems, especially when the carbapenems are administered by drug provocation testing (4,5,13,37,38). Aztreonam is the prototypical monobactam antibiotic. It is very weakly cross-reactive in the penicillin-allergic patient and may be administered safely to most patients allergic to other β-lactam antibiotics (74). The antibodies generated are specific to the side chain rather than the β-lactam ring. It should be noted, however, that ceftazidime, a third-generation cephalosporin, shares an identical side chain with aztreonam. It may be prudent not to use ceftazidime in rare subjects allergic to aztreonam (4). Loracarbef, a carbacephem, structurally resembles cefaclor, but the degree of cross-reactivity with penicillins and cephalosporins is unknown. Finally, clavulanic acid is also a β-lactam antibiotic with weak antibacterial activity but is a potent inhibitor of β-lactamase. It is combined with amoxicillin to enhance antimicrobial activity. There are reports of allergic reactions from clavulanic acid without allergy to amoxicillin (75,76).

Diagnostic Testing

Although obtaining and recording a past history of penicillin allergy is essential, one cannot completely rely on that information to predict who is allergic. The history may be inaccurate as coincidental chronic urticaria (35), anaphylaxis (76), and rashes (76) may have been the basis for patient's self-reporting drug allergy. Other patients lose their allergic reactivity over time (27,76). For example, in assessing patients with penicillin allergy, the patients found allergic by skin testing/drug provocation testing had a median time from the index

reaction of 1.5 years compared with 20 years for those patients who were no longer found allergic (76). Alternatively, the dismissing of the allergic reaction or outright failure to elicit this information or not entering the information into the medical record has resulted in fatalities following the administration of these drugs to patients with a history of β-lactam hypersensitivity (77). To help clarify this situation, when the drug is essential, skin testing with penicillin has been useful to identify those patients at risk for anaphylaxis and other, milder IgE-mediated reactions (4,5,13). When appropriate skin testing reagents are either unavailable or have not been validated, induction of drug tolerance/drug provocation testing with the desired β-lactam antibiotic is recommended (4,5,13).

Benzylpenicillin (BP) has a molecular weight of 300 and transforms (is not metabolized) in large part (about 95%) into a penicilloyl hapten moiety. This transformation product is referred to as the major determinant and has been conjugated to poly-D-lysine to form penicilloyl-polylysine (PPL). It is commercially available as Pre-Pen (manufactured by Allerquest, Plainville, CT and marketed by Alk-Abello) for skin testing. Other penicillin transformation products, including BP itself, constitute 5% or less of administered penicillin and are collectively referred to as the *minor determinant mixture* (MDM). They are minor in name only but are responsible for some penicillin anaphylactic reactions. A standardized MDM is not available commercially for skin testing and remains an unmet need. Therefore, a solution of BP (10,000 units/mL) has been used for skin testing purposes. Skin testing with both PPL and BP (as the sole minor determinant) should detect 85% to 88% of potential reactors (13,28). The 2010 Drug Allergy practice parameter stated, "Skin testing with the major determinant and penicillin G only (without penicilloate or penilloate) may miss up to 20% of allergic patients, but data on this are conflicting" (4). Almost all patients (99%) with negative skin tests to PPL and MDM reagents, including BP, can be treated safely with penicillin (21,28). If PPL is not used but MDM is, from 34% to 60% of skin test–positive patients would be missed (21). Thus, the major determinant identifies a significant proportion of skin test–positive patients, and its use improves safety during testing and desensitization. With the PPL and MDM, the negative predictive value of skin testing with major and minor determinants is as high as 99% (21,28) compared with about 40% to 66% with MDM only (21).

In general, skin testing with BP-derived reagents, PPL and MDM, is also predictive of reactions to other β-lactam antibiotics (21); however, there are occasional patients with reactions to ampicillin, amoxicillin, and cephalosporin

side chains who may not be detected by skin testing (62–64). Although skin testing with the β-lactam antibiotic of therapeutic choice has been advocated to detect additional potential reactors, skin test reagents prepared from other penicillins, cephalosporins, imipenem, and aztreonam have not been standardized, and the results are not validated. A positive skin test using these materials suggests the potential for an IgE-mediated reaction, but a negative test does not eliminate this concern. The incidence of such reactions to other β-lactam antibiotics when skin tests are negative to penicillin major and minor determinant reagents is probably low (21). Some MDMs are not as sensitive as others and have led to confusion about the need to detect side-chain–specific IgE.

In practice, penicillin skin testing to evaluate the potential of or current risk for an IgE-mediated reaction should be reserved for patients with a history, suggesting penicillin allergy when administration of the drug is essential or when confusion about penicillin allergy interferes with optimal antibiotic selection. Such testing is of no value in predicting the occurrence of non–IgE-mediated reactions and is relatively contraindicated when the previous reaction was Stevens–Johnson syndrome, toxic epidermal necrolysis (TEN), or exfoliative dermatitis. Elective penicillin skin testing followed by an oral challenge and subsequent 10-day course of treatment with penicillin or amoxicillin in skin test–negative subjects has been recommended, particularly in children with a history, suggesting penicillin allergy (78). It was hoped that this procedure would eliminate the need to carry out such testing when the child is ill and in need of penicillin therapy. Using this approach, the risk for resensitization was about 1%. In one small study of 19 patients, 16% of penicillin history–positive, but skin test–negative adults receiving intravenous penicillin therapy became skin test positive 1 to 12 months after completion of treatment (79). In another study, none of 33 penicillin history–positive, skin test–negative adults had evidence of IgE-mediated reactions, suggesting persisting loss of antipenicillin IgE antibodies (80). In this series of 568 patients with penicillin allergy and negative skin tests, only 1 of 33 patients, who were tested after the initial therapeutic course that resulted in a reaction, became skin test positive (80). These data suggest that reactions are not always IgE mediated and that resensitization appears to be very low. The overall data support the use of penicillin skin tests in managing patients with a history of penicillin allergy, regardless of the severity of the previous reaction. Penicillin skin testing is rapid, and the risk for a serious reaction is minimal when performed by proficient personnel, using recommended drug concentrations, and completing skin-prick tests before

attempting intradermal skin tests. Testing should be completed shortly before administration of the drug. However, in the absence of commercially available penicillin skin test reagents, the only option is to identify patients at higher risk than the normal population and perform drug provocation testing with caution.

Table 17B.2 summarizes the reagents used for β-lactam antibiotic skin tests and the recommended starting concentrations of these reagents, which are adequately sensitive but have a low risk for provoking a systemic or nonspecific irritant reaction. In patients with a history of a life-threatening reaction to penicillin, it may be advisable to dilute the skin test reagents 100-fold for initial testing. Skin-prick testing is accomplished by pricking through a drop of the reagent placed on the volar surface of the forearm and observing for 15 to 20 minutes. A significant reaction is a wheal 4 mm or larger than the control with surrounding erythema. If negative, proceed with intradermal skin tests. Using a tuberculin or an allergy syringe, inject 0.01 to 0.02 mL of the reagent, sufficient to raise a 2- to 3-mm bleb on the volar surface of the forearm. After 15 to 20 minutes, a positive test produces a wheal of 4 mm or larger with surrounding erythema. If the results are equivocal or difficult to interpret, the tests should be repeated. It should be noted that there is some disagreement among investigators as to what constitutes an acceptable positive skin test. A 4-mm wheal with surrounding erythema is positive; a 4-mm or greater wheal without erythema is "indeterminate" and usually not representative of antipenicillin IgE antibodies. Caution is required on test dose challenges though.

TABLE 17B.2 β-LACTAM ANTIBIOTIC SKIN TESTS

SKIN TEST REAGENTS	DRUG TEST ROUTE	SKIN TEST CONCENTRATION	TEST VOLUME	DOSE
Penicilloyl-polylysine[a] (Pre-Pen) (6×10^{-5} M)	Prick	Full strength	1 drop	
	Intradermal	Full strength	0.02 mL	
Penicillin G[a] potassium (freshly prepared)	Prick	10,000 U/mL	1 drop	200 units
	Intradermal (serial 10-fold dilutions optional)[d]	10,000 U/mL	0.02 mL	
Penicillin minor determinant mixture[b]	Prick	Full strength	1 drop	

$(10^{-2}$ M)	Intradermal (serial 10-fold dilutions optional)[d]	Full strength	0.01–0.02 mL	
Cephalosporins and other penicillins[c]	Prick	3 mg/mL	1 drop	60 µg
	Intradermal (serial 10-fold dilutions optional)[d]	3 mg/mL	0.02 mL	
Aztreonam[c]	Prick	3 mg/mL	1 drop	60 µg
	Intradermal (serial 10-fold dilutions optional)[d]	3 mg/mL	0.02 mL	
Imipenem[c]	Prick	1 mg/mL	1 drop	20 µg
	Intradermal (serial 10-fold dilutions optional)[d]	1 mg/mL	0.02 mL	
Histamine (Histatrol)—positive control	Prick	1 mg/mL	1 drop	
	Intradermal	0.1 mg/mL	0.02 mL	
Saline or diluent—negative control	Prick	NA	1 drop	
	Intradermal	NA	0.02 mL	

[a] Testing validated.

[b] Testing validated; reagents not available (except at some medical centers).

[c] Testing not validated. Negative tests do not rule out possibility of a reaction.

[d] Serial skin tests may be prudent when previous reaction was anaphylactic in nature.

Because penicillin MDM are not commercially available in the United States, and skin testing with other β-lactam antibiotics has not been standardized, nor have the results been validated, drug provocation testing is recommended in

patients with a past history of penicillin allergy. How one approaches this procedure depends on the severity of the previous reaction, the extent of the patient's anxiety, and the experience of the managing physician or health care professional. After documenting the need for the drug, obtaining informed verbal or written consent, and being prepared to treat anaphylaxis, a graded drug provocation test may be initiated with a physician in constant attendance; 0.001 mg (equivalent to 1.8 units of BP) of the therapeutic β-lactam antibiotic is administered by the desired (oral, intravenous) route. The patient is observed for signs of pruritus, flushing, urticaria, dyspnea, and hypotension. In the absence of these signs, at 15-minute interval, subsequent doses are given as outlined in Table 17B.3. If a reaction occurs during this procedure, it is treated with epinephrine intramuscularly and antihistamines; the need for the drug should be reevaluated and actual desensitization considered if this agent is essential. This is a rather conservative test-dosing schedule. More experienced physicians may elect to shorten this procedure; one suggestion has been to test dose with 1/100 of the therapeutic dose (1/1,000 of the therapeutic dose if the previous reaction was severe) and then increase toward the full therapeutic dose if there is no evidence of urticaria, flushing, wheezing, or hypotension (13).

TABLE 17B.3 SUGGESTED TEST-DOSING SCHEDULE FOR β-LACTAM ANTIBIOTICS

DOSE (mg)[a]	DOSE (units)[a]
0.001	1
0.005	10
0.01	20
0.05	100
0.10	200
0.50	800
1	1,600

10	16,000
50	80,000
100	160,000
200	320,000

Full dose may be administered.

[a] 400,000 units penicillin G potassium is roughly equivalent to 250 mg of other β-lactam antibiotics (1 μg = 1.8 units).

Because there is a small risk associated with skin testing and test dosing, *in vitro* tests have obvious appeal. Initially, solid-phase immunoassays, such as the radioallergosorbent test (RAST), which is no longer used, and the enzyme-linked immunosorbent assay, have been developed to detect serum IgE antibodies against the major penicilloyl determinant. The RAST or fluorescent immunoassay generally correlates with skin testing to PPL. Fluorescent immunoassays for cephalosporins and other antimicrobial drugs have been reported, but *in vitro* tests have limited-to-no clinical usefulness.

Management of Patients with a History of Penicillin Allergy

Preferable management of patients with a history of penicillin or other β-lactam antibiotic allergy is the use of an equally effective, non–cross-reacting antibiotic. In most situations, adequate substitutes are available, and consultation with infectious disease experts is valuable. Aztreonam, a monocyclic β-lactam antibiotic, has no clinical cross-reactivity with penicillins or cephalosporins and can be administered to patients with prior anaphylactic reactions to penicillin (4).

If alternative drugs fail, or if there is known antibiotic resistance by suspected pathogens, skin testing and drug provocation testing with the β-lactam antibiotic of choice should be performed. If skin tests are positive, if the patient reacts to test doses, or if such testing is not done, administration of the β-lactam antibiotic, using drug provocation testing, is advised (4–6,13). One begins with a subanaphylactic dose so that if anaphylaxis occurs, it can be controlled. For example, doses less than 1 mg would not be expected to induce anaphylaxis.

Some infections in which this approach becomes necessary include

enterococcal infections, brain abscess, bacterial meningitis, sepsis with staphylococci, *Neisseria* or *Pseudomonas* species organisms, *Listeria* infections, endocarditis, osteomyelitis, neurosyphilis, and syphilis in pregnant women. In fact, penicillin desensitization is indicated for pregnant women with syphilis who demonstrate immediate hypersensitivity to that drug (13). Also, at present, there are no data to support the use of alternatives to penicillin during pregnancy for treatment of primary, secondary or early latent neurosyphilis, and all stages of syphilis among HIV/AIDS-infected patients (13). With a target dose of 2,400,000 units of benzylpenicillin G, the starting dose is 0.1 unit subcutaneously, followed by 1, 10, 100, 1,000, 10,000, and 100,000 units. Then, 200,000 units are administered intramuscularly, followed by 2,100,000 units by the same route (13). This protocol delivers the 2,400,000 units for the initial dose (13). Then, assuming the initial treatment has been tolerated without any allergic manifestations, the 2,400,000 units of BP is administered in 1 week, without additional skin testing or drug provocation testing.

Another scenario involves a patient who presents with a convincing history of penicillin allergy and the physician has no available skin tests or proficiency with testing with BP, Pre-Pen, and/or MDM. Therefore, the drug provocation testing, as previously outlined, is recommended. If a reaction occurs at any test dose, the need for the drug should be reevaluated. If essential, an actual desensitization (drug provocation testing) protocol should be considered. A more unusual scenario is a patient with a positive history and available penicillin skin tests. Penicillin history–positive patients are at significant risk for anaphylaxis, but the level of current risk can be clarified by the presence or absence of positive immediate skin tests for penicillin determinants. The drug provocation testing (desensitization) protocols significantly reduce the risk for anaphylaxis in skin test–positive patients, whereas deliberate infusion of a β-lactam antibiotic at the usual rate could cause a severe or fatal anaphylactic reaction.

Although these graded drug provocation challenges can be performed in an outpatient facility, some true β-lactam antibiotic desensitizations should be performed in a monitored or an intensive care setting. Informed consent (verbal or written) is advised. Patients with asthma or congestive heart failure should be under optimal control. Premedication with antihistamines and corticosteroids is not recommended, because these drugs have not proved effective in suppressing anaphylaxis and could mask mild allergic manifestations that may have resulted in a modification of the desensitization protocol. It is believed that the early recognition of flushing and limited urticarial lesions during desensitization (or graded drug challenge) would alert the physician to the evidence of mast cell

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activation and risks involved. Suppression of the flushing or limited urticaria might result in a more serious, subsequent allergic reaction.

Before initiation of true desensitization, one intravenous line in a large vein is established; baseline vital signs are recorded. The clinical state of the patient is assessed. A baseline electrocardiogram and spirometry have been advocated by some as well as continuous electrocardiographic monitoring depending on the patient's comorbidities. During true desensitization, vital signs and the clinical state of the patient are noted before each dose, and at 10- to 20-minute interval following each dose. A physician must be in close attendance during the entire procedure so that unexpected reactions, such as hypotension, can be reversed quickly.

Desensitization has been accomplished successfully using either the oral or intravenous routes of administration (4,81–83). Oral desensitization is favored by some who believe that the risk for a serious reaction is less. The intravenous route is chosen by others, including myself, who prefer absolute control of the drug concentration used and its rate of administration. Unfortunately, there is no completely standardized regimen, and there have been no direct comparative studies between oral and intravenous desensitizing protocols.

Regardless of the method chosen for desensitization, the basic principles are similar. The initial dose is typically 1/10,000 of the therapeutic dose. Oral desensitization may begin with the dose that is tolerated during oral test dosing. Intravenous desensitization should begin with 1/10 or 1/100 (if the previous reaction was severe) of the dose producing a positive skin test or intravenous test dose response. The dose is then usually doubled at 7- to 15-minute interval until full therapeutic doses are achieved, typically within 4 to 5 hours. Representative protocols for intravenous (Table 17B.4) and oral (Table 17B.5) desensitization are presented.

Table 17B.4 outlines an intravenous desensitization protocol for penicillin G potassium or any other β-lactam antibiotic (13). The dose to be administered is placed in a small volume of 5% dextrose in water for piggyback delivery into the already established intravenous line. It is administered slowly at first, then more rapidly if no warning signs, such as pruritus or flushing, appear. If symptoms develop during the procedure, the flow rate is slowed or stopped and the patient treated appropriately, using the other intravenous site if necessary. After symptoms subside, the flow rate is slowly increased once again. Once the patient has received and tolerated 800,000 units of penicillin G or 800 mg of any other β-lactam antibiotic, the full therapeutic dose may be given and therapy continued

without interruption.

Table 17B.5 provides a protocol for oral desensitization with β-lactam antibiotics. If the patient is unable to take oral medication, it may be administered through a feeding tube. Mild reactions during desensitization, such as pruritus, fleeting urticaria, mild rhinitis, or wheezing, require the dose to be repeated until tolerated. If a more serious reaction occurs, such as hypotension, laryngeal edema, or severe asthma, the next dose should be decreased to at least one-third of the provoking dose and withheld until the patient is stable. If an oral form of the desired β-lactam agent is unavailable, intravenous desensitization should be considered. Once desensitized, treatment must not lapse. Regardless of the route selected for desensitization, mild reactions, usually pruritic rashes, may be expected in about 0% to 30% of patients during and after the procedure. These reactions usually subside with continued treatment, but symptomatic therapy may be necessary.

After successful desensitization, some individuals may have predictable needs for future exposures to β-lactam antibiotics. Patients with cystic fibrosis, chronic neutropenia, or occupational exposure to these agents may benefit from chronic twice-daily oral penicillin therapy to sustain a desensitized state between courses of high-dose parenteral therapy (83). However, some investigators are concerned about the ability to maintain 100% compliance among cystic fibrosis patients in an outpatient setting and, therefore, prefer to perform intravenous desensitization each time β-lactam antibiotic therapy is required (84).

TABLE 17B.4 PROTOCOL FOR INTRAVENOUS DESENSITIZATION WITH β-LACTAM ANTIBIOTICS

β-LACTAM CONCENTRATION (mg/mL)	PENICILLIN G CONCENTRATION (units/mL)	DOSE NO.[a]	AMOUNT GIVEN (mL)	DOSE GIVEN (mg/units)
0.1	160	1	0.10	0.01/16
		2	0.20	0.02/32
		3	0.40	0.04/64
		4	0.80	0.08/128

1	1,600	5	0.15	0.15/240
		6	0.30	0.30/480
		7	0.60	0.06/960
		8	1.00	1/1,600
10	16,000	9	0.20	2/3,200
		10	0.40	4/6,400
		11	0.80	8/12,800
100	160,000	12	0.15	15/24,000
		13	0.30	30/48,000
		14	0.60	60/96,000
		15	1.00	100/160,000
1,000	1,600,000	16	0.20	200/320,000
		17	0.40	400/640,000
		18	0.80	800/1,280,000

Observe patient for 30 minutes; administer full therapeutic dose intravenously.

[a]Dose approximately doubled every 7 to 15 minutes.

Adapted from Adkinson NF Jr. Drug allergy. In: Middleton EJ, Reed CE, Ellis EF, et al, eds. *Allergy: Principles and Practice*. 5th ed. St. Louis: CV Mosby; 1998:1212–1224.

In summary, β-lactam antibiotics can be administered by drug provocation testing (4,5,13) (induction of drug tolerance) with relatively little risk in most patients with a history of allergy to these drugs and a positive reaction to skin testing (13). Once successfully desensitized, the need for uninterrupted therapy is advisable until treatment has been completed. Any lapse in therapy greater than 12 hours may permit such sensitivity to return. Mild reactions during and after drug provocation testing are not an indication to discontinue treatment. Many such reactions resolve spontaneously or may require symptomatic therapy.

Among successfully desensitized patients with a positive history of β-lactam allergy and a positive response to skin testing or drug provocation testing, this same approach may be repeated before a future course of therapy. There appears to be little risk for resensitization following an uneventful course of therapy among patients with positive histories and negative skin tests or after uneventful test dosing (80). During drug provocation testing, which included true desensitization, there must be preparedness for anaphylaxis and its treatment. In the absence of skin testing, which helps to place the patient at high risk (if positive) and very low risk (if negative), patients with penicillin allergy are often undergoing drug provocation testing as opposed to actual desensitization. Nevertheless, when beginning the administration, without skin test results, the risk is based on the history and patient's comorbidities, including ineffectively controlled asthma or sepsis, as opposed to more precise data, such as the presence or absence of antipenicillin (BP, Pre-Pen, or MDD) IgE antibodies.

TABLE 17B.5 PROTOCOL FOR ORAL DESENSITIZATION WITH β-LACTAM ANTIBIOTICS

β-LACTAM CONCENTRATION (mg/mL)[a]	DOSE NO.[b]	AMOUNT GIVEN[c] (mL)	DOSE GIVEN (mg)
0.5	1	0.10	0.05
	2	0.20	0.10
	3	0.40	0.20
	4	0.80	0.40
	5	1.60	0.80

	6	3.20	1.60
	7	6.40	3.20
5	8	1.20	6
	9	2.40	12
	10	4.80	24
50	11	1.00	50
	12	2.00	100
	13	4.00	200
	14	8.00	400

Observe patient for 30 minutes; give full therapeutic dose by route of choice.

[a] Dilutions prepared from antibiotic syrup, 250 mg/5 mL.

[b] Dose approximately doubled every 15 minutes.

[c] Drug amount given in 30 mL water or flavored beverage.

Adapted from Sullivan TJ. Drug Allergy. In: Middleton EJ, Reed CE, Ellis EF, et al, eds. *Allergy: Principles and Practice*. 4th ed. St. Louis: CV Mosby; 1993:1726.

Non–β-Lactam Antimicrobial Agents

Allergic reactions to non–β-lactam antimicrobial drugs, most commonly cutaneous eruptions, are common causes of morbidity and, rarely, mortality. Anaphylaxis to these agents is a rare event. The estimated overall incidence of a hypersensitivity-type reaction to non–β-lactam drugs is about 1% to 3%. Some antimicrobial agents, however, such as TMP-SMX, produce reactions more commonly; in contrast, others, such as tetracycline, are much less likely to do so.

Unlike the β-lactam antimicrobials, other antibiotics have been less well studied and also include a wide variety of chemical agents. Research has been hampered by the lack of information regarding the immunochemistry of most of these drugs and, therefore, the unavailability of proven immunodiagnostic tests to assist the physician and health-care professional. Although skin testing with the free drug and some *in vitro* tests has been described for sulfonamides, aminoglycosides, and vancomycin, there are no large series reported to validate their clinical usefulness. The use of pharmacogenomic data prospectively should permit more precise "personalized medicine" and result in fewer adverse reactions.

Despite these shortcomings, when such agents, notably TMP-SMX, are medically necessary, protocols have been developed to administer these drugs (6,13,16). With the exception of sulfonamides and occasionally other non–β-lactam drugs, urgent administration is usually not required. Slow, cautious test dosing is generally a safe and effective method to determine whether the drug is now tolerated. An example is with TMP-SMX, where one can use the suspension containing 40 mg TMP and 200 mg SMX per 5 mL (4,13,85). The first dose is with 0.1 mg orally of the dose for SMX and, at 30- to 60-minute interval, administer 1, 10, and 50 mg. If there is no reaction, on the following day, 100 and 200 mg may be given. On occasion, particularly in life-threatening pneumocystis or toxoplasma infections in HIV/AIDS patients, an every 4-hour dosing schedule may be required. Because most reactions to non–β-lactam antimicrobial agents are nonanaphylactic (IgE independent), desensitization is indicated rarely and may be quite dangerous, as described later. Cutaneous eruptions from TMP-SMX typically occur on days 7 to 12 into treatment in patients with HIV/AIDS (4).

Sulfonamides

Background

The stimulus for continued attention to sulfonamide and TMP hypersensitivity is because of their utility in treatment of a wide variety of Gram-positive and Gram-negative bacterial infections and to their importance in the acute or empiric treatment of infectious complications in patients with HIV/AIDS or immunosuppression. In patients infected with HIV and living in poor countries, TMP-SMX may be used as prophylaxis and primary therapy for *Pneumocystis pneumonia,* as prophylaxis for *Toxoplasma gondii* infections, and as treatment for *Isospora belli* gastroenteritis. The combination of sulfadiazine and pyrimethamine is available for treatment of chorioretinitis and encephalitis due

to toxoplasmosis in HIV-positive patients. Sulfasalazine, which is a prodrug of 5-aminosalicylic acid (5-ASA) and the carrier molecule, sulfapyridine, balsalazide which is a prodrug for mesalamine, and olsalazine, another prodrug for mesalazine, may be used in the management of inflammatory bowel disease.

The most common reaction ascribed to sulfonamide hypersensitivity is a generalized rash, usually maculopapular in nature, developing 7 to 12 days after initiation of treatment. Fever may be associated with the rash. Urticaria is occasionally present, but anaphylaxis is a rare event. The TMP-SMX may have been associated with acute urticaria or other immediate reaction. Although it is often considered to be from SMX, anaphylaxis and allergic reactions have been attributable to TMP (86–89). In addition, severe cutaneous reactions, such as Stevens–Johnson syndrome and TEN, may occur from TMP-SMX (4,5,13) (see Chapter 16). Hematologic reactions, notably thrombocytopenia and neutropenia, serum sickness–like reactions, as well as hepatic and renal complications, may occur occasionally.

Diagnostic Testing

There are no *in vivo* or *in vitro* tests available to evaluate the presence of sulfonamide allergy. However, there is evidence that some of these reactions are mediated by an IgE antibody directed against its immunogenic metabolite, N^4-sulfonamidoyl (89). Further, studies using multiple N^4-sulfonamidoyl residues attached to polytyrosine carrier as a skin test reagent have been reported, but additional studies are necessary to evaluate its clinical usefulness (90). Most sulfonamide reactions are not IgE mediated (4,5,91–94). One notion is that most adverse reactions are caused by hydroxylamine metabolites, which induce *in vitro* cytotoxic reactions in peripheral blood lymphocytes of patients with sulfonamide hypersensitivity (95–98) Pharmacogenetics explain some adverse reactions because there are wide variations in acetylation, for example, slow acetylators experiencing more adverse reactions. The enzyme arylamine *N*-acetyltransferase 2 has multiple polymorphisms that account for variations in acetylation status (99) From 45% to 70% of SMX is acetylated to *N*-acetylsulfamethoxazole, with little oxidized to hydroxylamine (98,100). The hydroxylamine becomes nitrosulfamethoxazole and can result in cytotoxic effects (91–93,98,100). It is thought that low glutathione stores facilitate cellular injury because of an inability to limit the effects of reactive nitroso metabolites (98,100).

Clinical confirmation of sulfonamide reaction is accomplished by drug provocation testing (4,5,13,94). This is of concern particularly when treating

HIV/AIDS patients with TMP-SMX and also with the use of sulfasalazine or other prodrugs in the management of inflammatory bowel disease.

Management of Sulfonamide Reactions in Patients with HIV/AIDS

Patients infected with HIV/AIDS are at increased risk for hypersensitivity reactions to certain drugs (4,5,13,85–88,100). The best-known example of a drug that produces hypersensitivity reactions in such patients is TMP-SMX. Before the highly active antiretroviral therapy (HAART) era and in areas of the world where TMP-SMX is used widely, the following data are noteworthy: cutaneous eruptions from TMP-SMX occur in 3.4% of medical inpatients and in 29% to 65% of patients with HIV/AIDS being treated for *P. pneumonia* with this drug (93). The frequency of reactions to TMP-SMX has been reported also as 5% in HIV-negative subjects and up to 60% in HIV-positive subjects (4,94). Adverse reactions to TMP-SMX have been reported to be more likely when the CD4 count is greater than 20×10^6 cells/L, the CD4/CD8 is less than 0.10, and acetylation status is slow (100). The pathogenesis of these reactions is multifactorial (100). It is recognized that the SMX moiety is responsible for most of the cutaneous reactions, although TMP may be a cause of acute urticaria or anaphylaxis (86–88).

With a reasonable or definite history of a previous reaction, the preferred approach is to use alternative drugs. Pentamidine is a much less desirable alternative and is also associated with serious adverse reactions, such as pancreatitis. The recognized hyperallergic state of HIV/AIDS regarding allergic-type medication reactions has been documented for various HAART modalities, such as mevirapine and atazanavir (100). Cautious readministration of antiviral medications becomes an important consideration. Some protocols for HAART involve graded drug challenge over 36 hours to 5 days as opposed to full-dose rechallenge.

When TMP-SMX is indicated, one graded schedule SMX begins with administration of 1/100 of the full dose on day 1, 1/10 on day 2, 3/10 on day 3, and the full dose on day 4 (4,5,13,21). By taking several days to complete, delayed reactions may become evident. When more urgent administration is necessary, TMP-SMX has been given intravenously in doses of 0.8, 7.2, 40, 80, 400, and 680 mg (based on the SMX component) at 20-minute interval (94). Drug provocation testing (desensitization) may be performed with the pediatric suspension of TMP-SMX (5 mL contains 40 mg TMP and 200 mg of SMX) (6). The first dose is 0.05 mL (0.01 of a reduced adult dose). More prolonged courses of oral test dosing, such as 10 and 26 days, have been described (95,96). Delayed

reactions may be treated with 30 to 50 mg of prednisone daily and antihistamines to permit completion of the course of therapy for PJP. In one study, when the history was rash or rash and fever, a 5-day oral course was successful in 14 of 17 patients (97).

Test dosing with intravenous pentamidine has been successfully performed when there is a history of a previous reaction to this agent. A stock solution containing 200 mg pentamidine in 250 mL dextrose in water (0.8 mg/mL) is prepared. Starting with a 1:10,000 dilution of this solution, 2 mL is given intravenously over 2 minutes. At 15-minute interval, 2 mL of 1:1,000, 2 mL of 1:100, and 2 mL of 1:10 dilution are administered. After this, 250 mL full-strength solution is given over 2 hours. Successful treatment with aerosolized pentamidine in patients with adverse reactions to systemic pentamidine has been reported using a rapid test dosing schedule (101).

There are reports of anaphylactic-like reactions in patients with previous TMP-SMX–induced cutaneous reactions. Oral desensitization with TMP-SMX has been described, beginning with 0.00001 mg (SMX component) and progressing to full-dose treatment in 7 hours. This procedure is rarely indicated and is dangerous.

When TMP-SMX is indicated in HIV/AIDS patients in whom there has been a previous reaction to this medication, oral graded challenge such as over 36 hours to 5 days followed by daily administration has been effective but may reintroduce a rash. In such cases, prednisone is utilized to minimize the rash and continue the TMP-SMX. Bullous lesions are a contraindication to continuing the TMP-SMX.

Sulfadiazine, together with pyrimethamine, may be indicated for treatment of toxoplasmosis in HIV/AIDS patients. Among patients who react to sulfadiazine, clindamycin and pyrimethamine are less satisfactory alternatives for treatment of *T. gondii* encephalitis or chorioretinitis. Should this fail, rapid test dosing with sulfadiazine can be accomplished by using 1, 10, 100, 500, 1,000, and 1,500 mg at 4-hour intervals (102). Delayed cutaneous reactions can be treated with prednisone in an effort to complete the recommended course of therapy.

A history of Stevens–Johnson syndrome is nearly always an absolute contraindication to test dosing or desensitization with TMP-SMX (6,13,94,102). However, at times, the exact medication or infection causing the Stevens–Johnson syndrome is not known with confidence of certainty. It is known that cautious drug provocation testing can be performed after receiving consent. One successful approach was described in two patients with previous Stevens–

Johnson syndrome, when treated with TMP-SMX after an 8-day protocol beginning with 1 mL of 1:1,000,000 dilution of TMP-SMX suspension (103). Only in extreme circumstances should such a procedure be performed.

Management of Sulfasalazine Reactions in Patients with Inflammatory Bowel Disease

The active therapeutic component in sulfasalazine is 5-ASA, which is linked by an azobond to sulfapyridine. After oral ingestion, sulfasalazine is delivered intact to the colon, where bacteria split the azobond to release 5-ASA, which acts topically on inflamed colonic mucosa. (5-ASA may be administered as a suppository for ulcerative proctitis.) The sulfapyridine component is absorbed systemically and accounts for most of the adverse effects attributed to sulfasalazine. The drug has been used for mildly or moderately active ulcerative colitis, for maintaining remission of inactive ulcerative colitis and for some cases of Crohn disease. Oral 5-ASA preparations (e.g., olsalazine, mesalamine, or prodrug balsalazide) are first-line agents because of their superior side-effect profile and equivalent therapeutic efficacy compared with sulfasalazine (104). These medications also have a role in Crohn disease and possibly as a chemoprotective agent for colorectal cancer (104).

For the occasional patient with possible drug allergy who requires sulfasalazine, a slow graded challenge has been published (105). This approach starts with a dilute suspension of the drug (liquid sulfasalazine suspension diluted with simple syrup) and advancing the dose slowly, as shown in Table 17B.6 (105). If a rash or fever develops, the dose may be reduced and then advanced more slowly. This approach is ineffective for nonallergic toxicity (headache, nausea, vomiting, and abdominal pain) and should not be considered in patients who have had severe reactions, such as Stevens–Johnson syndrome, TEN, agranulocytosis, or fibrosing alveolitis. Most patients were able to achieve therapeutic doses, although some patients did require several trials.

With aminosalicylate preparations and corticosteroid enemas (budesonide), the use of other immunosuppressive drugs or immunomodulators, the medical management of inflammatory bowel disease will continue to improve, and, consequently, the need for sulfasalazine should continue to decrease.

TABLE 17B.6 TEST DOSING WITH SULFASALAZINE[a]

DAY	DOSE (mg)
1	1

2	790	2
3		4
4		8
5–11		10
12		20
13		40
14		80
15–21		100
22		200
23		400
24		800
25–31		1,000
32 above		2,000

[a]Patients should have failed newer anti-inflammatory agents.

Adapted from Purdy BH, Philips DM, Summers RW. Desensitization for sulfasalazine rash. *Ann Intern Med*. 1984;100:512.

Other Antimicrobial Agents

Aminoglycosides

Despite the introduction of newer, less toxic antimicrobial agents, the aminoglycosides continue to be useful with multiple indications. These agents have considerable intrinsic toxicity, namely, nephrotoxicity and ototoxicity.

Hypersensitivity-type reactions to aminoglycosides are infrequent and minor, usually taking the form of benign skin rashes or drug-induced fever. Anaphylactic reactions are rare but have been reported after tobramycin and streptomycin administration. Intravenous tobramycin has caused acute respiratory failure requiring intubation. Successful desensitization to tobramycin (18,106,107), colistin (108), and streptomycin (2) has been accomplished. In case reports, desensitization to tobramycin occurred with nebulized administration (18) and for colistin (8, 16, 24, 32, 40, and 80 mg every 30 minutes to reach the target of 80 mg) (108).

Vancomycin

Vancomycin is an important treatment for serious infections in patients with hypersensitivity reactions to β-lactams or in whom there is suspected or known bacterial resistance to β-lactam antibiotics.

Except for the "red-man" or "red-neck" syndrome, adverse reactions to vancomycin are relatively rare. Red-man syndrome is characterized by pruritus and erythema or flushing involving the face, neck, and upper torso, occasionally accompanied by hypotension. This has been attributed to the nonimmunologic release of histamine (109). This complication may be minimized by administering vancomycin, 1,000 mg, over at least a 1- to 2-hour period. Otherwise 1,000 mg of vancomycin administered over 30 minutes or less will cause mast cell histamine release (109). When a patient has ongoing pruritus from chronic renal failure or a dermatologic condition, a slower infusion (over 5 hours) of 500 mg or 1 g is recommended (110). In addition, pretreatment with antihistamines (e.g., cetirizine) may be protective.

Vancomycin has been reported to cause Stevens–Johnson syndrome/TEN (111–113), exfoliative dermatitis (113–115), IgA bullous dermatitis (113), and DRESS (113). When the exfoliative dermatitis has been generalized erythroderma with desquamation, drug provocation testing should be avoided in most patients except in the most demanding circumstances. Vancomycin-associated Stevens–Johnson syndrome should be differentiated from linear IgA bullous dermatosis (112). Acute interstitial nephritis from vancomycin has been reported (113).

Fluoroquinolones

Fluoroquinolones are valuable antimicrobial agents with a broad range of activity against both Gram-negative and Gram-positive organisms. Skin rashes and pruritus have been reported in less than 1% of patients receiving these drugs. Phototoxicity may occur. Rarely, Achilles tendon inflammation or rupture occurs. Anaphylactoid reactions, following the initial dose of fluoroquinolones or within the first 3 days of treatment, have been described (32,116–120). Cross-reactivity within the family of fluoroquinolones was high at 43%—of 7 patients) (120) and 27.3% (9 of 33 patients) (119). Should drug provocation testing be indicated, it is advisable to initiate the challenge with 0.1 or 0.01 of the targeted dosage (13).

Tetracyclines

Tetracyclines (including the semisynthetic, minocycline, and doxycycline) are bacteriostatic agents with broad-spectrum antimicrobial activity. They share a common ring structure but have different side chains. Morbilliform rashes, urticaria, and anaphylaxis (121–123) occur very rarely with tetracycline drugs. Doxycycline and demeclocycline may produce a mild-to-severe phototoxic dermatitis; minocycline does not. Photosensitivity may occur with all tetracycline drugs.

Chloramphenicol

With the availability of numerous alternative agents and the concern about toxicity, this drug is used infrequently. In patients with bacterial meningitis and a history of severe β-lactam hypersensitivity, chloramphenicol is an alternative choice, after ceftriaxone test dosing. For treatment of rickettsial infections in young children or pregnant women, when tetracycline is contraindicated, chloramphenicol has been utilized.

Bone marrow aplasia is the most serious toxic effect. Believed to be idiosyncratic, occurring in 1 in 40,000 cases of therapy, it tends to occur in patients who undergo prolonged treatment, particularly if the drug has been administered on multiple occasions. This might suggest an immunologic mechanism, but this has not been established. Skin rash, fever, and eosinophilia are observed rarely. Anaphylaxis has been reported (124,125) even from topical, ophthalmologic application (125).

Macrolides

Erythromycin is one of the oldest antibiotics and is infrequently prescribed. Side effects include nausea and vomiting. Hypersensitivity-type reactions are uncommon, and they consist of usually benign skin rashes, fever, eosinophilia,

or acute urticaria and angioedema. Anaphylaxis to oral erythromycin, 500 mg, has been reported (126). Cholestatic hepatitis occurs infrequently, most often in association with erythromycin estolate. Recovery is expected on withdrawal of the drug, although it may require a month or so to resolve.

The widely prescribed macrolides, azithromycin and clarithromycin, are better tolerated and less toxic. Fatal anaphylaxis from clarithromycin (127) and nonfatal anaphylaxis from telithromycin (128) and azithromycin (129) have been reported. Some cases of hepatic failure have limited the use of telithromycin, a bactericidal macrolide. Cholestatic hepatitis has been reported with these three macrolides (130–132), and substituting one for another is not recommended because liver injury is assumed to be a class effect (130).

Clindamycin

This drug is active against most anaerobes, most Gram-positive cocci, and certain protozoa. The main concern with clindamycin use is *Clostridium difficile* pseudomembranous colitis. Adverse drug reactions to clindamycin occurred in less than 1% of hospitalized patients (133). Urticaria, drug fever, eosinophilia, and erythema multiforme have been reported occasionally. Anaphylactic shock is extremely rare (134,135).

Metronidazole

Metronidazole is useful against most anaerobes, certain protozoa (*Trichomonas vaginalis*), and *Helicobacter pylori*. The most common adverse reactions are gastrointestinal. Hypersensitivity reactions, including urticaria, pruritus, and erythematous rash, have been reported as has anaphylaxis (136,137). There is a case report of successful oral desensitization in a patient after what appeared to be an anaphylactic event (138).

Antifungal Agents

Allergic reactions to amphotericin B are quite rare. A report described a patient with amphotericin B-induced anaphylaxis (139). The patient was successfully challenged intravenously with amphotericin, using a desensitization-type protocol. Acute stridor during testing with amphotericin B may occur and require racemic epinephrine (140). Liposomal amphotericin is not necessarily safer than amphotericin B in terms of nephrotoxic effects. Anaphylactic reactions have been reported in patients receiving liposomal preparations (141–144), including a fatality (143). In a series of 141 treatments in children, 2(1.4%) anaphylactic reactions occurred (144). Other adverse effects include elevation of liver enzymes, increased serum creatinine, and electrolyte wasting (hypomagnesemia

and hypokalemia) (144).

Hypersensitivity-type reactions, notably rash and pruritus, occur with azoles. A case of anaphylactic shock from ketoconazole on the fourth day of administration has been reported with a tryptase concentration of 35 ng/mL (145). Itraconazole has been associated with generalized maculopapular rash and rarely anaphylaxis (146). There is a description of successful oral desensitization to itraconazole in a patient with localized coccidioidomycosis (147). Rarely, urticaria (posaconazole) (148) and angioedema (voriconazole) (149) occur. Overall, the adverse effects from the azoles (itraconazole, ketoconazole, voriconazole, and posaconazole) consist of the possibility of drug interactions (potentiation of effects), hepatotoxicity, and visual change (150).

The echinocandin class of antifungals (caspofungin and micafungin) can result in infusion associated flushing, pruritus, urticaria (151), other rashes, or anaphylaxis (152). Infusion related reactions to caspofungin have been attributed to its inhibition of histamine degradation by blocking activity of *N*-methyltransferase (151).

Antiviral Agents

Hypersensitivity reactions to HAART agents are very common among HIV-infected patients (100). There is a report of a patient who was successfully desensitized to zidovudine using a protocol requiring 37 days (153) and a shorter, 10-day protocol (154). A 7-hour desensitization was successful in a patient with efavirenz allergy (155). The patient twice had developed a generalized maculopapular, pruritic rash with efavirenz, 600 mg. The true induction of drug tolerance (drug provocation test or desensitization) began with 1:20,000 of the target dosage (155).

In a patient with allergic-type cutaneous reactions to both acyclovir and fancyclovir, successful graded challenge with acyclovir was reported. The starting dose was 2 mg with doubling to reach 200 mg (156). One patient was described with reproducible generalized urticaria from valacyclovir with tolerance of acylovir (157). Of note, there is a case report of the very successful benefit of valacyclovir that was administered for genital herpes that seemed to trigger outbreaks of cholinergic urticaria (158).

The neuraminidase inhibitors, oseltamivir, laninamivir, peramivir, and zanamivir, inhibit both influenza A and B viruses and infrequently cause rashes or erythema (159). Life-threatening bronchoconstriction can occur with zanamivir. Patients with asthma should receive zanamivir with caution (160) if at

all. The M2 protein channel inhibitors, amantadine and rimantadine, are considered quite safe (161).

Acute tongue and pharyngeal swelling with urticaria, stridor, and hypotension has been reported with another antiviral agent, lamivudine (162). Ichthyosiform eruptions and urticarial rashes have also been reported (163).

Antituberculous Agents

Many manifestations of hypersensitivity resulting from antituberculous drugs usually appear within 3 to 7 weeks after initiation of treatment. The most common signs are fever and rash, and the fever may be present alone for a week or more before other manifestations develop. The skin rash is usually morbilliform but may be urticarial, purpuric, or rarely exfoliative. Less common manifestations include a lupus-like syndrome (especially with isoniazid). Anaphylaxis rarely has been associated with streptomycin, ethambutol, rifampin (164), and moxifloxacin (164).

A common approach is to discontinue all drugs (usually isoniazid, rifampin, pyrazinamide, and moxifloxacin) and allow the reaction (usually a rash) to subside. Subsequently, each drug is reintroduced by test dosing to identify the responsible agent. Another drug then may be substituted for the causative agent. Another approach has been to suppress the reaction with an initial dose of 40 to 80 mg of prednisone daily while antituberculous therapy is maintained. This has resulted in prompt clearing of the hypersensitivity reaction, and with adequate chemotherapy, steroids do not appear to affect the course of tuberculosis unfavorably. After taking prednisone for several weeks, the corticosteroid preparation may be discontinued, and the reaction may not reappear.

Adverse drug reactions often may be attributable to isoniazid, rifamycins, ethambutol, and moxifloxacin because these medications can cause severe hypersensitivity reactions (165,166). There is a case report of DRESS with streptomycin (166).

Multiple Antibiotic Intolerance (Allergy) Syndrome

Patients who have reacted to any antimicrobial drug in the past have as high as a 10-fold increased risk for an allergic reaction to another antimicrobial agent (167). The multiple drug intolerance syndrome is characterized by the report of allergic reactions to medications in three structurally different classes (168). The physician should be aware of this possibility and be prepared for such and institute prompt treatment. Alternatively, patients with chronic neurodermatitis (purigo nodularis), chronic or sporadic idiopathic urticaria, dermatographism,

high levels of anxiety or if "allergic to all known drugs" may confuse pruritus or idiopathic urticaria with new onset of drug hypersensitivity (61). Drug provocation testing can be informative to determine the current level of risk. However, empiric suppression of baseline pruritus and rash is helpful with up-dosing of H_1 antihistamines before the administration of incriminated medications.

Aspirin and Other Nonsteroidal Anti-Inflammatory Drugs

Background

Aspirin (ASA) and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) rank second or third to the β-lactam antibiotics in producing "allergic-type" drug reactions. Unpredictable reactions to these agents include (a) acute bronchoconstriction in some patients with nasal polyps and persistent asthma (aspirin exacerbated respiratory disease [AERD], formerly Aspirin Triad or Samter syndrome; (b) an exacerbation of urticaria in 20% to 30% of patients with idiopathic urticaria or angioedema; (c) anaphylactic reactions with a threat to life, and (d) acute urticaria and/or angiodema (169). When patients are challenged, the reaction often occurs with less than 100 mg of aspirin within 3 hours of ingestion (170). During aspirin challenge, between 66% and 97% AERD patients will have positive responses (170). Among otherwise normal individuals, anaphylactic and urticarial reactions have occurred within minutes after the ingestion of a full dose of ASA or a nonselective NSAID. For some patients, it is a particular, single NSAID that causes the reaction (169). Although ASA has been recommended to treat indolent systemic mastocytosis, there is a subset of patients with this disorder who experience either acute urticaria/angioedema or anaphylactic reactions after the ingestion of ASA and nonselective NSAIDs. Aspirin and nonselective NSAIDs may be cofactors for food-dependent exercise-induced anaphylaxis, angioedema from angiotensin-converting enzyme (ACE) inhibitors, and oral mite anaphylaxis (171,172).

The typical AERD patient is an adult with persistent asthma and chronic rhinosinusitis, often with nasal polyps. The onset of asthma may have been in childhood. In other words, such patients have had established persistent asthma for years before the first clear episode of an ASA-induced respiratory reaction occurs in adulthood. Such reactions usually occur within 2 hours after the ingestion of ASA or a nonselective NSAID, and may be quite severe and rarely fatal. The reaction may be associated with profound nasal congestion, rhinorrhea, and ocular injection.

Currently, one of the more attractive hypotheses to explain these ASA- and NSAID-induced respiratory reactions stems from the observation of pharmacology that these drugs share the property of inhibiting the generation of cyclooxygenase-1 products, such as prostaglandin E_2, thereby permitting the synthesis of lipoxygenase products, most notably leukotriene-D_4 (LTD_4). LTD_4 causes acute bronchoconstriction and increases vascular permeability. To support this assertion, the 5-lipoxygenase inhibitor, zileuton, has been shown to block the decline in forced expiratory volume at 1 second (FEV_1) after ASA ingestion among ASA-sensitive asthmatic patients (173). Also, after aspirin challenge, there is a 10-fold increase in urine LTE_4 concentration, reflecting heightened synthesis of LTD_4 (174). Furthermore, patients with ASA-sensitive asthma are hyperresponsive to LTE_4 given during bronchoprovocation; indeed, they are hypersensitive by a factor of 13 compared with ASA-tolerant patients with asthma (170,174). Drugs that block cyclooxygenase-1 reduce production of prostaglandin E_2, originally recognized as a bronchodilator. However, it has a critical "braking" effect on the generation of leukotrienes by inhibiting 5-lipoxygenase and 5-lipoxygenase-acting protein (170). Thus, nonselective NSAIDs reduce the production of this critical "braking" prostaglandin.

The selective cyclooxygenase-2 antagonists, celecoxib and refecoxib, have been tolerated uneventfully in nearly all aspirin-intolerant patients with asthma to date (4,5,13,169,170,175,176). Test challenges in a supervised setting do not appear necessary.

A subpopulation of patients with *chronic idiopathic (spontaneous) urticaria or angioedema* experiences an exacerbation of urticaria after ingesting ASA or nonselective NSAIDs (177). Using appropriate challenge techniques, the prevalence is between 20% and 30% (169). A reaction is much more likely to occur when the urticaria is active at the time of challenge (177). Avoidance of these agents eliminates acute exacerbations of urticaria following their ingestion but appears to have little effect on the ongoing chronic idiopathic urticaria. Some patients experience delayed onset (>24 hours) rashes from nonselective NSAIDs (176).

The prevalence of *anaphylactic* (formerly called *anaphylactoid*) *reactions* after the ingestion of both ASA or specific NSAIDs is unknown. Characteristically, such patients appear to be normal and react to only one NSAID or to ASA (169,176). Cross-reactivity within the entire class of cyclooxygenase-1 inhibitors is rare in these patients. Further, some such

reactions occur after two or more exposures to the same NSAID (169,176). These features suggest the possibility of an IgE-mediated response, but specific IgE against ASA or any NSAID has not been demonstrated. On occasion, urticaria or angioedema alone may occur after the ingestion of ASA or a nonselective NSAID in patients without ongoing chronic urticaria. It is advisable to have patients avoid all nonselective NSAIDs (and aspirin) unless it has been demonstrated that a specific nonselective NSAID is the sole cause of anaphylaxis or urticaria or angioedema (13).

Diagnostic Tests

The diagnosis can usually be established by history and does not require confirmatory testing. On occasion, there may be circumstances in which the diagnosis is unclear or a confirmed diagnosis is required. Skin tests are of no value in the diagnosis of ASA or NSAID sensitivity. Also, there are currently no reliable *in vitro* tests available for the detection of ASA sensitivity. The only definitive diagnostic test is test dosing (4,5,13,169,170,176).

Among patients with asthma, test dosing with ASA or nonselective NSAIDs can provoke a severe acute respiratory reaction and should be attempted only by experienced physicians capable of managing acute, severe asthma in an appropriate medical setting. Nebulized albuterol and/or intramuscular epinephrine should be available. The asthma should be under optimal control before test dosing is begun. The possible high risk for this procedure must be considered in relation to its potential benefit. The FEV_1 should be at least 60% of predicted, and the respiratory status of the patient must be stable. A detailed description of a 3-day test dosing protocol may be found elsewhere (10). A typical starting dose of ASA is 3 mg, and progresses to 30, 60, 100, 150, 325, and 650 mg at 3-hour intervals if there is no reaction (10). If a reaction occurs, subsequent ASA challenges are suspended, and the reaction is treated vigorously. A shorter approach is beginning with intranasal ketorolac as follows: prepare ketorolac (60 mg/2 mL) mixed with preservative free saline 2.75 mL in an empty nasal spray unit (178). On day 1, begin with one spray each nostril, if no or <15% decline in FEV_1, give two sprays each nostril in 30 minutes, then four sprays each nostril in 30 minutes, and six sprays each nostril after another 30 minutes. Observe for 60 minutes for respiratory signs and 15% decline of FEV_1. If none has occurred or if there is <15% reduction of FEV_1, give aspirin 60 mg; wait 90 minutes, then give another 60 mg. Observe for 3 hours. On day 2, begin with 150 mg; observe 3 hours, then give 325 mg. Observe 3 hours (178). A decline of peak nasal inspiratory flow of >25% is also consistent with a

positive challenge.

After an ASA-induced respiratory reaction, there is a 2- to 5-day refractory period during which the patient may tolerate ASA and all other nonselective NSAIDs (179). Although not currently available in the United States, ASA-lysine has been used for inhalation challenge to verify ASA-sensitive asthmatic patients in Europe (180). Considering the potential difficulties with test dosing and the fact that ASA and other nonselective NSAIDs can be avoided, such diagnostic challenges should be reserved for patients with suspected sensitivity to ASA or nonselective NSAIDs who now require those agents for management of chronic conditions.

For patients with suspected or proven coronary or carotid artery disease and intermittent episodes of or chronic idiopathic (spontaneous) urticaria, provocation drug testing may be performed in an outpatient setting. For those with ongoing urticarial lesions, treatment of the condition should be continued to avoid false-positive results. If the urticaria is intermittent, test dosing can be accomplished during a remission. One approach is to begin the challenge with 10 mg. If there is no urticaria or symptoms in the first 30 minutes, then administer 30 and 41 mg at 30-minute interval. At this point, the patient is observed for 90 minutes and if no objective evidence of urticaria or angioedema (or bronchoconstriction) has occurred, the patient can be released to home. If the target dosage is 81 mg daily, the patient continues that dosage. Otherwise, the dosage of aspirin can be 81 mg on day 2, 162 mg on day 3, 243 mg on day 4, and 325 mg on day 5, and thereafter. If the patient develops urticaria, it is difficult to ''treat through" or desensitize. Depending on the essentiality of aspirin therapy, a decision would be made as to whether such desensitization should be attempted.

Test dosing for anaphylactic reactions is seldom indicated and can be dangerous. However, as previously noted, anaphylactic reactions are limited usually to either ASA or a single nonselective NSAID. Therefore, test dosing with another NSAID may demonstrate its safety for use in treating a medical condition. When ASA administration is essential, other NSAIDs are unacceptable alternatives as platelet inhibitors. For this reason, the above suggested protocol is used during the oral ASA test challenge to reach an initial final dose of 81 mg.

Management of Aspirin- and Other Nonsteroidal Anti-Inflammatory Drug-Sensitive Patients

Once ASA and other NSAID sensitivity develops, it may last for years.

Therefore, strict avoidance of these drugs is critical. Patients should be attentive to the variety of commonly available nonprescription preparations that contain ASA or nonselective NSAIDs, such as "cold," headache, and analgesic remedies. All nonselective NSAIDs that inhibit the cyclooxygenase-1 pathway cross-react to varying degrees with ASA in causing respiratory reactions among ASA-sensitive asthmatic patients and in triggering urticarial reactions among patients with chronic idiopathic urticaria who react to ASA. A current list of NSAIDs that cross-react with ASA is provided in Table 17B.7.

Among ASA-sensitive patients, acetaminophen is most commonly recommended as an alternative and is almost always tolerated uneventfully. However, high doses of acetaminophen, such as 1,000 mg, were reported to provoke acute bronchoconstriction (decreases in FEV_1) in about one-third of ASA-sensitive asthmatic patients (181). In general, acetaminophen-induced respiratory reactions are much milder and of shorter duration than those induced by ASA. When asthma is stable, if necessary, test dosing with acetaminophen may be attempted starting with 325 mg. If there is no reaction after 2 to 3 hours, 650 mg is given. After 3 more hours, if there has been no adverse reaction, 1,000 mg of acetaminophen may be given (181). Salsalate is also a weak cyclooxygenase inhibitor, which has caused a decrease in FEV_1 in up to 20% of ASA-sensitive asthmatic patients when 2,000 mg is given (182). Salsalate and choline magnesium trisalicylate have no effect on cyclooxygenase-1 *in vitro* and do not cause acute bronchoconstriction in ASA-sensitive asthmatic patients in recommended doses. Although there was a report of a bronchoconstrictive reaction to hydrocortisone sodium succinate (Solu-Cortef) in 1 of 45 ASA-sensitive asthmatic patients (183), this occurrence seems exceedingly rare. Also, tartrazine (FD&C yellow dye) does not cross-react with ASA in ASA-sensitive patients or induce acute respiratory reactions, as was thought at one time (170).

TABLE 17B.7 STRONG INHIBITORS, WEAK INHIBITORS, AND NONINHIBITORS OF CYCLOOXYGENASE-1

STRONG INHIBITORS OF CYCLOOXYGENASE-1

Diclofenac (Voltaren, Arthrotec, Cataflam)

Diflunisal (Dolobid)

Etodolac (Lodine)

Fenoprofen (Nalfon)

Flubiprofen (Ansaid)

Ibuprofen (Motrin, Advil, Nuprin, Haltran, Medipren)

Indomethacin (Indocin)

Ketoprofen (Orudis, Oruvail)

Ketorolac (Toradol)

Meclofenamate (Meclomen)

Mefanamic acid (Ponstel)

Meloxicam (Mobic)

Nabumetone (Relafen)

Naproxen (Naprosyn, Anaprox, Aleve, Naprelan)

Oxaprozin (Daypro)

Piroxicam (Feldene)

Sulindac (Clinoril)

Tolmetin (Tolectin)

WEAK INHIBITORS OF CYCLOOXYGENASE-1 (SUITABLE, INITIAL ALTERNATIVES)

Acetaminophen (Tylenol, Datril, Excedrin, Midol, Percogesic)

Salsalate (Disalcid)

NONINHIBITORS OF CYCLOOXYGENASE-1

Choline magnesium trisalicylate (Trilisate)

Celecoxib (Celebrex)

Hydroxychloroquine (Plaquenil)

A practical problem is what advice to give to historically non–ASA-sensitive asthmatic patients regarding the use of ASA and other nonselective NSAIDs. One approach is to caution such patients about the potential for such a reaction, particularly if they have nasal polyps and are prednisone dependent. There is a low incidence of ASA sensitivity in most patients with asthma with normal computed tomography scans of the sinuses and in patients with clear evidence of IgE-mediated asthma. Treatment with ASA or other nonselective NSAIDs may be medically necessary in some patients with AERD, such as the management of

a rheumatoid or osteoarthritis or to inhibit platelet aggregation for coronary artery or carotid disease. Induction of drug tolerance (drug provocation testing) is identical to oral graded challenge with ASA or intranasal challenge with ketorolac for diagnostic purposes, except that the administration of ASA continues following a positive respiratory reaction. The dose of ASA that caused the reaction is reintroduced after the patient has recovered. If no further reaction occurs, at 3-hour intervals, the dose is gradually increased until either another reaction occurs or the patient can tolerate 650 mg of ASA without a reaction. Once successfully desensitized, cross-desensitization between ASA and all other nonselective NSAIDs is complete. This state can be maintained indefinitely if the patient takes at least one ASA dose daily; if ASA is stopped, it persists for only 2 to 5 days.

True ASA desensitization followed by long-term ASA treatment has been advocated for treatment of AERD, including for the chronic rhinosinusitis (10,184). Such treatment has resulted in improvement in rhinosinusitis with prevention of nasal polyp reformation and improved sense of smell, as well as allowing a significant reduction in the need for systemic and inhaled corticosteroids. Nevertheless, as with other antiasthma treatments, ASA desensitization does not induce a remission of persistent asthma. The target dosage is 650 mg twice daily, and this dosage may result in gastritis or gastrointestinal bleeding. Nevertheless, patients may benefit if they can tolerate the long-term aspirin at this dosage (170,184).

Unlike AERD, ASA-sensitive urticaria and angioedema do not appear to respond to ASA desensitization as consistently (177). Aspirin desensitization has been employed to prevent synthesis of mast cell–derived prostaglandin D_2, a cyclooxygenase-1 product thought to be largely responsible for systemic reactions, among patients with indolent systemic mastocytosis, who in fact, have experienced anaphylactic reactions after the ingestion of ASA or nonselective NSAIDs.

Acetaminophen

In contrast to the rare AERD patient who develops a 25% to 33% decrease in FEV_1 with a 1,000 mg challenge with acetaminophen (181), true anaphylactic reactions to acetaminophen have been reported (185–188). The provoking doses necessary to induce shock were described as 125, 191, and 300 mg (185–187). Elevated plasma or urine histamine concentrations were demonstrated (185,187). These patients were not ASA sensitive and had anaphylactic reactions, as compared with the rare AERD patient who has a moderate bronchoconstrictive

response to 1,000 mg of acetaminophen.

Concurrent acetaminophen and aspirin sensitivity was reported in a 13-year-old girl with asthma (189). She experienced acute urticaria, angioedema, and dyspnea within 10 minutes of ingesting 650 mg of acetaminophen. Aspirin, 325 mg, and indomethacin, 300 mg, caused acute urticaria (189). Such sensitivity must be exceedingly rare. For practical purposes, AERD patients can use acetaminophen in recommended doses (500 to 650 mg) without initial test dosing.

Radiographic Contrast Media

Background

Radiographic contrast media (RCM) are clear solutions and should not be called "dyes." Nonfatal immediate generalized reactions (most commonly urticaria) occur in 2% to 3% of patients receiving conventional ionic high-osmolality RCM and in less than 0.5% of patients receiving the lower osmolality agents. A large prospective study reported severe life-threatening (often anaphylactic) reactions occurring in 0.22% of those receiving the high-osmolality media compared with only 0.04% of those receiving lower osmolality preparations (190). It is clear that the lower osmolality RCM causes significantly fewer adverse reactions (191–194), but severe or fatal reactions may occur (195,196). In fact, the risk for a fatal reaction may be the same with either class of RCM and is estimated to be 0.9 cases per 100,000 infusions (191). Deaths have occurred with all types of RCM (57,191). The volume infused in fatal reactions may be less than 10 mL in some cases (191).

The overall prevalence of reactions to the noniodinated, gadolinium-based contrast agents for magnetic resonance imaging is about 0.1% based on 204 adverse reactions in a study of 194,400 intravenous administrations (197). There were no deaths and just one case of anaphylactic shock (197). There were two other cases of diffuse erythema with hypotension that could seem compatible with anaphylaxis. Allergic-type reactions occur less frequently, such as reported to be about 0.07% (1:1,451 injections) (198,199) to 0.15% (1:667 injections) (200). Severe systemic reactions to these agents were reported in 1:19,588 injections (198). Pretreatment with prednisone-diphendydramine does not always prevent reactions to gadolinium-based contrast agents (197,198), but experience is limited.

Clearly, there are patients at increased risk for an immediate generalized (anaphylactic) reaction to iodinated RCM. The most obvious and important risk

factor is a history of a previous reaction to these agents. The exact reaction rate is unknown, but with ionic hyperosmolality RCM, it ranges between 17% and 60% (194). The administration of nonionic lower osmolality agents to such patients reduces the risk to 4% to 5.5% (201,202). Severe coronary artery disease, unstable angina, advanced age, female sex, and receipt of large volumes of contrast media are also risk factors (191). Atopic individuals and asthmatic patients appear to be more susceptible to anaphylactic reactions to RCM (190,191,203). There is some disagreement about the risk for an anaphylactic reaction to RCM among patients receiving β-adrenergic blocking agents (204,205). The risk was not found to be increased in frequency or severity in a prospective study (204); however, reactions may be more severe and less responsive to treatment in patients with cardiac impairment. Among such patients, the use of lower osmolality RCM and possibly pretreatment with antihistamines and corticosteroids (discussed later) may be advisable. The data that patients who have reacted to topical iodine cleansing solutions and iodides and those allergic to shellfish are at slightly increased risk for RCM reactions were based on use of older, higher osmolality RCM (206). In facilities, where administration of lower osmolality RCM is standard practice, patients with a history of shellfish allergy or "iodine" allergy do not have to be pretreated (191,207,208) unless, in my opinion, there is a high level of anxiety about the procedure that cannot be abated during an explanation with the patient.

Typically, most anaphylactic reactions from iodinated RCM begin within 1 to 3 minutes after intravascular administration, very rarely after 20 minutes. Nausea, emesis, and flushing are most common and may be caused by vagal stimulation. Such reactions are to be distinguished from anaphylactic reactions, which include pruritus, urticaria, angioedema, bronchospasm, hypotension, and syncope. Urticaria is the most common reaction. Most of these reactions are self-limited and respond promptly to the administration of epinephrine and antihistamines. However, the potential for a fatal outcome must not be ignored, and trained personnel must be available to recognize and treat hypotension and cardiac or respiratory arrest. Sudden-onset grand mal seizure likely reflects cerebral hypoperfusion and not epilepsy. Delayed-type reactions begin from 30 to 60 minutes up to 1 week and often are maculopapular rashes or urticaria (191).

The mechanism of RCM-induced acute and anaphylactic reactions remains incompletely understood. These reactions are not clearly IgE mediated but involve histamine release from mast cells and basophils, tryptase and other mediator release from mast cells, generation of bradykinin via activation of

clotting factor XII, and generation of nitric oxide (NO) by activation of L-arginine (191). Complement can be activated even in the absence of clinical manifestations (191).

Diagnostic Testing

There are no *in vivo* or *in vitro* tests to identify potential reactors to RCM (191). Severe and fatal reactions have occurred after an intravenous test dose of 1 to 2 mL. Also, severe reactions have followed a negative test dose. Graded test dosing has been abandoned.

As noted previously, a history of a previous reaction to RCM is the most valuable information necessary to assess the risk for a repeat reaction (191,194).

Management of Patients at Increased Risk for a Repeat Radiographic Contrast Media Reaction

Among patients with a previous reaction to iodinated RCM, the incidence and severity of subsequent reactions has been reduced using pretreatment regimens of corticosteroids, H_1 antihistamines, and adrenergic agents and employing lower osmolality as compared to high-osmolality RCM. Using older higher osmolality RCM, pretreatment with prednisone and diphenhydramine reduced the prevalence of repeat reactions to about 10%, whereas the addition of ephedrine to this protocol reduced it further to 5% (209). The addition of lower osmolality RCM to the prednisone-diphenhydramine regimen decreased the incidence of repeat reactions even further to 0.5% (194). Most repeated reactions tended to be quite mild.

The following summarizes a useful approach that can be recommended when patients with a history of an iodinated RCM-associated anaphylactic reaction require a repeated study (191,194):

1. Document in the medical record the need for the procedure and that alternative procedures are unsatisfactory.

2. Document in the record that the patient or responsible person understands the need for the test and that the pretreatment regimen may not prevent all adverse reactions.

3. Recommend the use of lower osmolality RCM if available.

4. Pretreatment medications (191,194) are as follows:

   A. Prednisone, 50 mg orally, 13, 7, and 1 hour before the RCM procedure.

   B. Diphenhydramine, 50 mg intramuscularly or orally, 1 hour before the

RCM procedure.

C. Albuterol, 4 mg orally, 1 hour before the RCM procedure (withhold if the patient has unstable angina, cardiac arrhythmia, or other cardiac risks).

5. Have emergency therapy available and proceed with the RCM study.

There may be situations in which high-risk patients require an emergency RCM study. The following emergency protocol is recommended (194,210):

1. Administer hydrocortisone, 200 mg intravenously, or methylprednisolone, 40 mg, intravenously, immediately, and every 4 hours until the study is completed.

2. Administer diphenhydramine, 50 mg intramuscularly, immediately before or 1 hour before the procedure.

3. Administer albuterol, 4 mg orally, immediately before or 1 hour before the procedure (optional).

Because several hours are required for corticosteroids to be effective, it is best to avoid the emergency administration of RCM unless absolutely necessary. The medical record should note that there has not been time for conventional pretreatment and that there is limited experience with such abbreviated programs.

It is also important to be aware that anaphylactic reactions to RCM may occur when these agents are administered by nonvascular routes, for example, retrograde pyelograms, hysterosalpingograms, myelograms, and arthrograms. Previous reactors undergoing those procedures should receive pretreatment as described previously.

Finally, it should be noted that the pretreatment protocols are useful only for the prevention of anaphylactic reactions, but not for other types of life-threatening reactions, such as ventricular tachycardia or fibrillation, the adult respiratory distress syndrome, or noncardiogenic pulmonary edema.

Patients with asthma should have their respiratory status stable under ideal circumstances. Similarly, isotonic hydration and perhaps acetylcysteine should be employed to prevent acute renal failure or increases in serum creatinine (191).

There is not sufficient data regarding effectiveness of these pretreatment protocols or patients who have experienced prior allergic reaction to gadolinium-based materials (191). There is no cross-reactivity between gadolinium-based chelates and iodinated RCM (191). It is my recommendation to administer the

pretreatment as above with the patient's consent.

Local Anesthetics

Background

Patients who experience adverse reactions of virtually any type following the injection of a local anesthetic may be advised erroneously that they are allergic to these agents and should never receive "caines" in the future. Such patients may be denied the benefit of dental care or a surgical procedure. A patient may experience a respiratory or cardiac arrest after receiving a local anesthetic with epinephrine injection for routine dental care. The likely explanation is acute cardiac ischemia from the 1:100,000 epinephrine being absorbed quickly into the sublingual veins. The patient may then develop apparent noncardiogenic "flash" pulmonary edema. Such patients are not truly reacting to the local anesthetic.

More commonly, adverse effects are vasovagal reactions, toxic reactions, hysterical reactions, or as noted, epinephrine-related effects. Allergic contact dermatitis is the most common immunologic reaction to local anesthetics. On occasion, clinical manifestations suggestive of anaphylactic reactions are described, but most reported series have shown that such reactions occur rarely, if ever (211–213). In one study, reproducible reactions were noted for articane and lidocaine (213).

As shown in Table 17B.8, local anesthetics may be classified as benzoic acid esters (group I) or others (group II). On the basis of local anesthetic contact dermatitis and patch testing studies, the benzoic acid esters often cross-react with each other but do not cross-react with those agents in group II. Also, drugs in group II do not cross-react with each other and appear to be less sensitizing.

It has been suggested that sulfites and parabens, which are used as preservatives in local anesthetics, may be responsible for allergic-like reactions. However, such reactions are so rare as to be reportable (214). When confronted with this remote possibility, the pragmatic approach is to avoid preparations containing them. On the other hand, latex-containing products, such as gloves and rubber dams, might have been used in dental and surgical practices. Local or systemic reactions may occur in latex-sensitive patients, and this possibility should be considered in the differential diagnosis of adverse reactions attributed to local anesthetic agents.

TABLE 17B.8 CLASSIFICATION OF LOCAL ANESTHETICS

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Diagnostic Testing

Initial skin testing as a part of a test-dosing protocol is the preferred approach. Prick tests are usually negative. Positive intradermal skin tests are often found in otherwise healthy controls and do not correlate with the outcome of test dosing (13,211–213). *In vitro* testing is not applicable.

Management of Patients with a History of Reactions to Local Anesthetics

If the local anesthetic agent causing the previous reaction is known, a different local anesthetic agent should be selected for administration for reassurance. For

example, if the drug is an ester, an amide may be chosen. If the drug is an amide, another amide may be used. Nevertheless, if lidocaine has been incriminated, it may be feasible to test with lidocaine for practical purposes.

The use of diphenhydramine might provide reasonable anesthesia required for suturing, but clearly this is inadequate for dental anesthesia.

Unfortunately, the local anesthetic agent is often unknown, and the clinical details of the previous reaction are often vague, unavailable, or of uncertain significance. For this reason, the following protocol has been effective in identifying a local anesthetic agent that the patient will tolerate (10):

1. Obtain verbal consent.

2. Determine the local anesthetic agent to be used by the dentist or physician. It must not contain epinephrine. These are usually available as ampules.

3. At 15-minute interval:

   A. Perform a skin-prick test using the undiluted local anesthetic.

   B. If negative, inject 0.1 mL of a 1:100 dilution subcutaneously in an extremity.

   C. If there is no local reaction, inject 0.1 mL of a 1:10 dilution of local anesthetic subcutaneously.

   D. If there is no local reaction, inject 0.1 mL of undiluted local anesthetic agent.

   E. If there is no local reaction, inject 1 mL and then 2 mL of the undiluted local anesthetic agent.

4. Following this procedure, a letter is given to the patient indicating that the patient has received 3 mL of the respective local anesthetic with no reaction and is at no greater risk for a subsequent allergic reaction than the general population.

5. Such test dosing should be undertaken by individuals with training and experience in such tests, and also in treatment of anaphylactic reactions.

This regimen should be completed before the anticipated procedure, and in some cases, it can be done to help exclude local anesthetic "allergy." To date, we are not aware of any patient with negative test dosing who reacted later when the local anesthetic agent was used for a procedure, with the exception of hysterical reactions. The success of this approach is undoubtedly related to the extreme

rarity of true allergic reactions to local anesthetic agents. However, at the least, the protocol serves to allay some or all of the anxiety of patients and referring dentists and physicians, and at the most, it may permit one to identify safely that rare patient truly at risk for an allergic reaction to subsequent local anesthetic administration.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Antagonists

ACE inhibitors have efficacy in treatment of patients with left ventricular systolic dysfunction or congestive heart failure, as secondary prevention in patients who have experienced a myocardial infarction, in diabetic patients, and as antihypertensive agents. ACE inhibitors have been reported to cause a nonproductive cough in 1% to 39% of patients; this cough subsides in a few days or in less than 4 weeks in some cases (215). The cough even may last up to 3 months (215). If there is a compelling rationale for reinstitution of the ACE inhibitor, readministration can be carried out (215). Alternatively, angiotensin receptor blockers don't cause the nonproductive cough (215).

Angioedema from ACE inhibitors has been recognized in other patients, perhaps with an incidence of 0.1% to 0.3% (172,216). The angioedema may cause massive tongue or pharyngeal swelling such that intubation is required. ACE-associated angioedema has a predilection for the tongue, pharynx, and face as opposed to gastrointestinal tract or as isolated dysphagia (172). It has been reported that first episodes occurred in the first 4 weeks of ACE inhibitor use in 22% of patients, and 77% occurred after that time, with an overall mean duration until presentation of 11 months (217,218). In another study, the mean time was 19 months, with a range of 3 days to 6.3 years (219). Sometimes, the onset is after 10 years (172). African Americans and people of Chinese origin appear to be at increased risk for experiencing angioedema from ACE inhibitors (172,215,216,219,220). Because 7 of 9 patients in one series were using aspirin, it has been hypothesized that aspirin could be a cofactor in ACE inhibitor angioedema (216). Nonselective NSAIDs may also be a cofactor (172). Complement is not consumed during these reactions.

ACE inhibitors have been reported to induce anaphylactic reactions during hemodialysis, especially when the dialysis membrane is polyacrilonitrile but not cuprophane or polysulfone (221–223).

ACE inhibitors have three substrates: bradykinin, substance P, and angiotensin I. The mechanism of acute angioedema is considered to be attributable to production of excessive bradykinin in that ACE inhibitors, which

block generation of angiotensin II from angiotensin I, also inhibit inactivation of bradykinin and substance P. The accumulation of bradykinin is thought to cause cough and angioedema and contribute to anaphylactic reactions by causing vasodilation via the bradykinin B_2 receptor. The major pathways for bradykinin degradation utilize ACE (bradykininase) and aminopeptidase P. ACE inhibitors decrease the metabolism of aminopeptidase P (172,224,225). There is a minor pathway for bradykinin degradation into des-Arg-bradykinin via action of carboxypeptidase *N* (172). Genetic differences in reactors appear to explain some episodes (224). It remains to be determined whether our current understanding is the correct explanation because acute angioedema from angiotensin II receptor blockers also occurs (225,226). And, at least in hypertensive patients, the angiotensin II receptor blocker, losartan, increased the concentrations of bradykinin, comparably to levels that occurred with the ACE inhibitor, captopril (227). Reactions to losartan have occurred within 1 day to 16 months after beginning the therapy (228). Some patients have never received an ACE inhibitor. Angiotensin II receptor blockers are not contraindicated in patients who have experienced angioedema from an ACE inhibitor, but physician awareness of potential future episodes is warranted (172,226).

Drugs that increase the likelihood of ACE inhibitor angioedema include dipeptidyl peptidase-4 inhibitor, vildagliptin, because it blocks the degradation of substance P and the bradykininase activity of dipeptidyl peptidase-4 (229). The absolute risk of angioedema is very small (229). The immunosuppressive drugs that inhibit the mammalian target of rapamycin can also lead to ACE inhibitor angioedema (226).

In patients with idiopathic anaphylaxis, hereditary angioedema, or acquired C1 esterase inhibitor deficiency, ACE inhibitors (and β-adrenergic antagonists) are contraindicated at least on a relative basis until our understanding of these reactions improves.

The treatment of ACE inhibitor–associated angioedema with icatibant, the competitive antagonist for the bradykinin B_2 receptor, has been reported as effective (230) and ineffective (231). With icatibant treatment of angiotensin receptor blocker angioedema, the recovery was 5 to 7 hours compared with 27 to 52 hours in prednisolone/clemastine treated and 24 to 54 hours in untreated patients (225).

Opiates

Opiates have their historic basis traced back 1,800 years ago related to opium

(232). Opioid receptors have been identified as μ, δ, κ, and nociceptin/orphanin FQ (232). The classic opioid actions are mediated by μ-receptor stimulation that results in analgesia, decreased gastrointestinal transit time, contraction of the sphincter of Oddi, respiratory depression, decreased cough, and pupillary constriction. Analgesia is caused by activation of μ, δ, and κ receptors. However, μ receptors are present in ascending nerves in the spinal tract and in the brain, whereas κ receptors are present only in spinal nerves. Morphine activates μ and κ receptors, whereas fentanyl acts on μ, δ, and κ receptors.

Morphine and codeine are most likely to activate mast cells and cause flushing or acute urticaria. Intravenous morphine could cause symptoms consistent with an anaphylactic reaction. Meperidine, tramadol, and fentanyl are ineffective triggers of mast cells. Meperidine is out of favor because of sharp rises and falls in serum concentrations; although it can cause diaphoresis, it is an unlikely cause of urticaria.

Patients may have confused opioid effects for hypersensitivity, but when there is a history of codeine- or morphine-induced urticaria, alternative agents may be selected if narcotics are required. For example, fentanyl can be administered intravenously or transdermally. Lower doses of long-acting formulations of morphine may be tried as well. Should a challenge with morphine become necessary, the following approach is suggested at 15-minute interval: subcutaneously 0.1 mg, then 0.5 mg, and finally 1 mg (13). If required, the dose can be increased to 2 mg and then 4 mg after determining any symptoms and need for analgesia.

Chemotherapy for Neoplastic Diseases

Many chemotherapeutic agents result in bone marrow suppression or other particular adverse effects, including serious cutaneous eruptions. Interstitial lung disease, infiltrates, or pulmonary fibrosis can occur with the use of bleomycin, methotrexate, cyclophosphamide, busulfan, carmustine; platinum derivatives (cisplatin and oxaliplatin); docetaxel; placitaxel; and all-trans-retinoic acid as examples (4,13,233–236). The latter has been associated with basophil-derived histamine release, causing acute bronchoconstriction when administered to patients with acute promyelocytic leukemia. The promyelocytes resemble basophils! Capillary leak syndromes occur with interleukin-2, cytosine arabinoside, the combination of mitomycin and vinca alkaloids and other agents. L-Asparaginase, docetaxel, and placitaxel can cause anaphylactic-type reactions (13). The stabilizer, Cremophor El is like Tween 80 and can be the explanation for the reactions (13). Premedication with corticosteroids and antihistamines can

reduce the number of reactions from paxlitaxel (13) and some other chemotherapeutic agents. When there is sensitization via production of IgE antibodies, desensitization is indicated (237). Reducing the rate of infusion may be of value in some patients.

Anaphylaxis has occurred with various chemotherapeutic agents, but fortunately it is rare. The platinum drugs, cisplatin and carboplatin, can cross-react and are potent sensitizers, which can cause anaphylactic-type reactions (238–240). Because many of these reactions are IgE mediated, prednisone-diphenhydramine pretreatment is not expected to be successful. If either of these agents is truly essential and the patient agrees, skin testing can be carried out with prick tests of 0.1 mg/mL concentration with intradermals of 0.001, 0.01, and 0.1 mg/mL (239). Desensitization should begin with 0.01 mg or less depending on the skin test results. In some cases, desensitization will be successfully carried out, but not in all cases. Indeed, as little as 3.5 mg of cisplatin has caused anaphylaxis (239). The physician must be in attendance with epinephrine available as described with desensitization protocols (4,5,13,237).

The taxanes come from the yew trees with paxlitaxel from the bark and docetaxel from the needles (237). Premedication with the corticosteroid, dexamethasone, the evening before, and $H_1 + H_2$ antihistamines 30 to 60 minutes preinfusion is recommended (237).

Desensitization for larger molecules, including monoclonal antibodies, is reviewed in Chapter 17C.

Anticonvulsants

The anticonvulsant hypersensitivity syndrome is rare but typically begins within 2 months of initiation of phenytoin, carbamazepine, phenobarbital, lamotrigine, or other anticonvulsants (241–251). In a few cases, the onset is in the third month of therapy. Reactions consist of fever, marked erythematous papules that may blister or demonstrate necrosis from vasculitis, and desquamate. Other findings include tender lymphadenopathy, liver enlargement, and oral ulcerations. The term *anticonvulsant hypersensitivity syndrome* clinically is referred to as DRESS. The author believes that such patients have sufficient criteria for the diagnosis of Stevens–Johnson syndrome, but DRESS is recognized as its own entity. In fact, in a series of patients with Stevens–Johnson syndrome, phenytoin, carbamazepine, valproic acid, lamotrigine, and phenobarbital were all identified among culprit medications. Associated laboratory findings may include atypical lymphocytes, eosinophilia, elevation of

serum creatinine, and liver function test abnormalities. Leukopenia may occur in some patients. Pulmonary eosinophilia with respiratory failure has been reported. The name of *anticonvulsant hypersensitivity syndrome* initially had been suggested because of the combination of fever, severe pruritic rash, and lymphadenopathy associated with multisystem involvement (252), but DRESS is preferred now. Some cases are familial (247). Carbamazepine may be more likely to cause the DRESS syndrome or Stevens–Johnson syndrome based on HLA-B genotypes (HLA-B*1502) primarily in Southeast Asians (244,245). This finding has not been confirmed in Caucasians (246). HLA-A*31:01 has been associated with carbamazepine-associated rashes among Europeans and Japanese people (253). Because of shared structures and metabolism, it is thought that when a patient develops the DRESS syndrome to either phenytoin or carbamazepine, that neither of these medications or phenobarbital should be readministered. When the diagnosis has not been clear or an error occurs, even a single additional dose of phenytoin or carbamazepine may elicit the DRESS or Stevens–Johnson syndrome in a susceptible patient. However, phenobarbital is not automatically contraindicated in patients allergic to phenytoin or carbamazepine (247). Challenges must be carried out in exceptional cases and with very small doses. However, when the rash was not necessarily part of DRESS syndrome, alternative anticonvulsants are often prescribed. The rate of cross-reactivity has been reported as follows: rash to phenytoin implied a rash to carbamazepine in 42%, phenobarbital in 19.5%, and lamotrigine in 18.9%; rash to carbamazepine implied a rash to phenytoin in 57.6%, to phenobarbital in 26.7%, and to lamotrigine in 20% (250).

The mechanism may relate to inadequate detoxification by epoxide hydrolase of hepatic microsome-generated metabolites of phenytoin and carbamazepine (241,242,247,248,251). The relatives of affected patients who are themselves nonepileptic and nonexposed to phenytoin may have findings of delayed metabolism (247). The metabolites are thought to cause either apoptosis or neoantigen formation with the clinical hypersensitivity syndrome (241,243,247). Sensitized $CD4^+$ T_H1, T_H2, and T_H17 lymphocytes, $CD8^+$ lymphocytes, and the presence of the skin-homing receptor, CLA, and type IV c immunologic hypersensitivity have been reported as findings in skin rashes and/or blistering (244,246). Genetic polymorphisms predispose Southeast Asians positive for HLA-B*1502 for carbamazepine-induced Stevens–Johnson syndrome and HLA-B*5701 for carbamazepine-induced Stevens–Johnson syndrome/TEN (244,245). As stated, this genotype has not been reproduced in some Caucasian people (246). Whatever the mechanism, systemic corticosteroids should be administered

and anticonvulsants discontinued (13) (see Chapter 16).

Alternative anticonvulsants, if necessary, should be selected, such as valproic acid, divalproex, phenobarbital, benzodiazepines, gabapentin, and topiramate. Valproic acid and divalproex are hepatotoxic, so caution is advised in patients with liver involvement. Appropriate neurologic consultation is advisable because of the high frequency of cutaneous reactions (250).

Muscle Relaxants

The neuromuscular blocking agents are categorized as depolarizing (succinylcholine) and nondepolarizing (atracurium, vecuronium, and pancuronium). The latter functions as reversible acetylcholine receptor antagonists. Acute anaphylactic reactions present as sudden-onset hypotension, shock, or acute bronchoconstriction with difficulty in ventilation by the anesthesiologist. Emergent intubation and cardiopulmonary resuscitation may be necessary. Generalized urticaria may or may not be reported, but flushing or angioedema may be observed on the face. Serum tryptase concentrations may be elevated as evidence of mast cell activation. The neuromuscular blocking agents may cause an IgE-mediated reaction or induce mast cell activation independent of IgE antibodies. Improvements in synthesis have resulted in agents with little ability to activate mast cells. In some cases, very rapid infusion of the agent causes an immediate reaction, whereas administration over 30 to 60 seconds does not. The incidence of anaphylactic reactions during general anesthesia may be in the range from about 1:5,000 to 1:25,000 (4,254–256). Up to 25% of reactions occur on the initial anesthetic exposure, which might be explained by the presence of quaternary and tertiary ammonium ions being present in cosmetics, disinfectants, foods, and other medications.

The nondepolarizing neuromuscular blocking agents have tertiary and quaternary ammonium groups that are considered to be the antigenic sites for IgE. Cross-reactivity exists based on skin test results. Skin testing begins with prick tests and then intradermal testing (4,5,13,254,257–259). The neuromuscular blocking agents must be diluted (13,254,257–259). For prick (epicutaneous) testing, dilutions for testing are as follows:

Pancuronium	1 mg/mL
Succinylcholine	20 mg/mL
Vecuronium	1 mg/mL

For intradermal testing, dilutions begin as follows:

Pancuronium	0.002 mg/mL	0.02 mg/mL	0.2 mg/mL
Succinylcholine	0.001 mg/mL	0.01 mg/mL	0.1 mg/mL
Vecuronium	0.004 mg/mL	0.04 mg/mL	0.4 mg/mL

If the prick test is negative, begin with the weakest dilution for intradermal testing. If the first intradermal skin test is negative, continue with stepwise skin testing until the highest strength is used. If it is also negative, the agent can be considered for administration. Incriminated agents include vecuronium, pancuronium, atracurium, cisatracurium, rocuronium, D-tubocurarine, and succinylcholine. Skin testing will identify cross-reactive agents, but some patients have immediate cutaneous reactivity to a single agent. Negative skin tests help identify the agents that can be administered safely.

The differential diagnosis of intraoperative anaphylaxis can be broad (4,5,13,254,255,256,260–262). Some examples include unrecognized or unappreciated latex allergy, the frequently administered empiric antibiotic, cefazolin (254), and rarely fentanyl (211), and protamine. Other agents, such as benzodiazepines, thiopental, propofol, and even chlorhexidine rarely, are proven to be etiologic (259,260,262). The hypnotic agent ketamine, which has sympathetic-stimulating actions, caused acute severe pulmonary edema in an 8-year-old child (261). After surviving intraoperative anaphylaxis, a very rare patient will be identified with heretofore undiagnosed indolent systemic mastocytosis (262).

Proton Pump Inhibitors/Histamine$_2$ Receptor Antagonists

Proton pump inhibitors and histamine$_2$ receptor antagonists are usually tolerated uneventfully, except for patients who experience diarrhea or other gastrointestinal side effects. Anaphylaxis has been reported with omeprazole (263–266) as well as successful drug provocation testing of the cumulative dose of 32 mg of omeprazole in 5.6 hours (265). Cross-reactivity by skin testing has been demonstrated between omeprazole and lansoprazole (263). Severe

erythroderma, erythema multiforme, and even TEN from proton pump inhibitors have been reported (267).

Stevens–Johnson syndrome has been described from ranitidine (268). In one patient, the target lesions, sublingual ulcers and conjunctivitis, began 1 day after a single raniditine tablet (268). The history was of uneventful exposure 2 years previously during a month of treatment and "itchy skin eruptions" on the forearms and legs 1 year previously. This patient's case reinforces the point that a single tablet of medication can induce Stevens–Johnson syndrome when the patient is sensitized (see Chapter 16).

Antiplatelet Therapy

Antiplatelet therapy is indicated for patients with acute coronary syndrome, coronary artery disease who may require angioplasty or coronary artery bypass grafting, and for patients who have undergone insertion of a newer generation stents (269). Dual-antiplatelet therapy consists of aspirin plus an antiplatelet drug. Often patients will be treated for 3 to 12 months or longer (269). Frequently administered antiplatelet drugs include clopidogrel, prasugrel, and ticagrelor (269) No longer distributed in the United States, ticlopidine had recognized adverse effects, including neutropenia and thrombocytopenic purpura. Clopidogrel has reduced incidence of such adverse effects but may cause pruritus, rash, angioedema, or anaphylaxis. Often, the pruritic rash from clopidogrel begins within the first 3 days to 1 month of therapy. It may be necessary to perform desensitization. Approaches include a protocol of 0.005, 0.010, 0.020, 0.040, 0.080, 0.160, 0.30, 0.60, 1.20, 2.50, 5.0, 10, 20, and 40 mg (270–272). Alternatively, it may be possible to begin with 0.30 mg and proceed every 30 minutes with an accumulated target dose of 75 mg. Depending on the rash that may occur during desensitization, prednisone and antihistamines may be required. In some cases, desensitization is not possible because the cutaneous eruption does not allow for continued clopidogrel administration.

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*Oral agents.

PART C

Immunologic Reactions to High-Molecular-Weight Therapeutic Agents

LESLIE C. GRAMMER

There are an increasing number of therapeutic agents that are proteins, including humanized monoclonal antibodies such as omalizumab and recombinant human proteins such as interferon α (IFN-α) (1). Therapeutic agents that are proteins, either of human or nonhuman origin, greater than 3 to 5 kDa, can be recognized by the human immunologic system and can cause sensitization and hypersensitivity reactions. Because these proteins are complete antigens, they can be used as skin testing reagents or as antigens in *in vitro* assays. Nonhuman protein hormones such as porcine insulin and adrenocorticotropic hormone are well-recognized causes of hypersensitivity reactions. Antithymocyte globulins (ATG), derived from rabbit or equine sources as well as equine antisera against rabies or botulinum toxin, have been reported to cause immediate-type I hypersensitivity as well as type III immune complex–mediated hypersensitivity. Nonhuman protein enzymes such as chymopapain and streptokinase have been reported to cause anaphylaxis and other milder hypersensitivity reactions (2). Unusual hypersensitivity reactions such as hand-foot syndrome have been reported with monoclonal antibodies, such as brentuximab (3).

Human recombinant proteins are less likely than nonhuman proteins to result in hypersensitivity reactions, but they do occur. Factors influencing the immunogenicity of proteins include frequency and duration of treatment, route of administration, and genetic background of the patient. A likely explanation for this somewhat unexpected occurrence is that the hypersensitivity reactions are caused by B-cell recognition of alteration in tertiary or quaternary structure. The

primary amino acid sequence, recognized by T cells, is an exact copy of the endogenously produced human protein and, therefore, does not initiate immunologic processes, such as hypersensitivity.

◼ INSULIN

Background

Insulin was the first recombinant human protein to which hypersensitivity reactions were reported, and thus can serve as a model for hypersensitivity reactions against high-molecular-weight agents. The exact incidence of insulin allergy is unknown; however, it appears to be on the decline (2). The increasing use of human recombinant DNA (rDNA) insulin may in part be responsible. However, it should be noted that human rDNA insulin has been associated with severe allergic reactions. Patients with systemic allergy to animal source insulin have demonstrated cutaneous reactivity to human rDNA insulin (4). In most patients, the anti-insulin antibody appears to be directed against a determinant present in all commercially available insulin (5).

Although about 40% of patients receiving porcine insulin developed clinically insignificant skin test reactivity to insulin, the prevalence of cutaneous reactivity in patients receiving human rDNA insulin is unknown. Immunologic insulin resistance because of anti-insulin immunoglobulin G (IgG) antibodies may follow or occur simultaneously with IgE-mediated insulin allergy (4). The most common, clinically important, immunologic reactions to insulin are local and systemic allergic reactions and insulin resistance.

Local allergic reactions are common; usually appear within the first 1 to 4 weeks of treatment; and consist of mild erythema, induration, burning, and pruritus at the injection site. Immediate, delayed, and biphasic IgE-mediated reactions have been described. Although most local allergic reactions disappear in 3 to 4 weeks with continued insulin administration, they may persist and may precede a systemic reaction. Discontinuing insulin because of local reactions may increase the risk for a systemic allergic reaction when insulin therapy is resumed. Treatment of local reactions, which is occasionally indicated, involves the administration of antihistamines as needed; in some cases, it may be useful to switch to a different preparation.

Systemic allergic reactions to insulin are IgE-mediated and are characterized by urticaria, angioedema, bronchospasm, and hypotension; such reactions are rare (6). Most commonly, these patients have a history of interruption in insulin

treatment. Systemic reactions occur most frequently within 2 weeks of resumption of insulin therapy and are often preceded by the development of progressively larger local reactions. It is most common to have a large urticarial lesion at the site of insulin injection. Most biologic agents are not given continuously. Perhaps that is one factor contributing to the relatively high frequency of hypersensitivity reactions to biologics.

Immunologic insulin resistance is even more rare than insulin allergy and is related to the development of anti-insulin IgG antibodies of sufficient titer and affinity to inactivate large amounts of exogenously administered insulin, generally in excess of 200 units daily. When nonimmune causes of insulin resistance such as obesity, infection, and endocrinopathies have been excluded, treatment involves the use of corticosteroids, for example, 60 to 100 mg prednisone daily. This is effective in the majority of patients, and improvement is expected during the first 2 weeks of treatment. The dose of prednisone is decreased gradually once a response has occurred, but many patients may require small doses, such as 15 mg on alternate days, for up to 6 to 12 months (5).

Management of Patients with Systemic Insulin Allergy

After a systemic allergic reaction to insulin, and presuming insulin treatment is necessary, insulin should not be discontinued if the last dose of insulin has been given within 24 hours. The next dose should be reduced to about one-third to one-tenth of the dose that produced the reaction, depending on the severity of the initial reaction. Subsequently, insulin can be increased slowly by 2 to 5 units/injection until a therapeutic dose is achieved (2). Very slow subcutaneous infusion insulin is another approach (7).

If more than 24 hours has elapsed since the systemic allergic reaction to insulin, desensitization may be attempted cautiously if insulin is absolutely indicated. The least allergenic insulin may be selected by skin testing with commercially available insulins. Table 17C.1 provides a representative insulin desensitization schedule (5). When no emergency exists, slow desensitization over several days is appropriate. The schedule may require modifications if large local or systemic reactions occur. In addition to being prepared to treat anaphylaxis, the physician must be prepared to treat hypoglycemia, which may complicate the frequent doses of insulin required for desensitization. More rapid desensitization may be required if ketoacidosis is present. The schedule suggested in Table 17C.1 may be used, but the doses are administered at 15- to 30-minute intervals.

TABLE 17C.1 INSULIN DESENSITIZATION SCHEDULE

DAY	TIME[a]	INSULIN (UNITS)	ROUTE[b]
1	7:30 AM	0.00001[c]	Intradermal
	12:00 noon	0.0001	Intradermal
	4:30 PM	0.001	Intradermal
2	7:30 AM	0.01	Intradermal
	12:00 noon	0.1	Intradermal
	4:30 PM	1.0	Intradermal
3	7:30 AM	2.0	Subcutaneous
	12:00 noon	4.0	Subcutaneous
	4:30 PM	8.0	Subcutaneous
4	7:30 AM	12.0	Subcutaneous
	12:00 noon	16.0	Subcutaneous
5	7:30 AM	20.0[d]	Subcutaneous
6	7:30 AM	25.0[d]	Subcutaneous

[a]Increase by 5 units/days until therapeutic levels are achieved; in ketoacidosis, the doses may be given every 15 to 30 minutes.

[b]Some physicians prefer to give all doses subcutaneously.

[c]Days 1 through 4: regular insulin.

[d]Days 5 and 6: neutral protamine hagedorn (NPH) or Lente insulin.

STREPTOKINASE AND OTHER ENZYMES

A variety of enzymes have been reported to cause IgE-mediated immediate-type reactions; the predictive value of skin tests has been reported to be especially high with chymopapain which is rarely used and streptokinase which is used for thrombolytic therapy in low-resource settings because it is cost effective (8,9).

However, such testing does not eliminate the possibility of a late reaction, such as serum sickness. Currently, thrombolytic therapy can be performed with recombinant tissue plasminogen activator (tPA), which very rarely has been associated with acute urticaria, angioedema, or anaphylaxis; prior use of angiotensin-converting enzyme inhibitors has been reported as a risk factor for angioedema occurring with tPA (10).

L-Asparaginase is an important therapy for certain types of leukemia. Those allergic to the *Escherichia coli*–derived product can often tolerate treatment with asparaginase from *Erwinia chrysanthemi* (11). Two human recombinant enzymes have not been associated with allergic reactions. Large trials with dornase alfa (12) and a small trial with agalsidase alfa (13) have not reported significant hypersensitivity.

LATEX

Latex is used in the manufacture of a variety of medical products, such as a urethral catheters and latex gloves. Latex is the natural milky rubber sap that is harvested from the rubber tree, *Hevea brasiliensis*. Latex allergy has been reported to cause type IV contact dermatitis and IgE-mediated reactions during procedures involving latex exposure. Fortunately, the incidence of hypersensitivity reactions is declining (14). Intraoperative anaphylaxis is now more likely to be caused by neuromuscular blocking agents or antibiotics than by latex (15).

Since 1979, when the first case of rubber-induced contact urticaria was reported, many instances of IgE-mediated hypersensitivity reactions have been described, including contact urticaria, rhinitis, asthma, and anaphylaxis. Contact urticaria is the most common early manifestation of IgE-mediated rubber allergy, particularly in latex-sensitive health-care workers, who report contact urticaria involving their hands. These symptoms are often incorrectly attributed to the powder in the gloves or frequent handwashing. Inhalation of latex-coated cornstarch particles from powdered gloves has evoked rhinitis and asthma in latex-sensitive people. Many of these individuals are atopic with a history of rhinitis caused by pollens and asthma caused by dust mites and animal dander (16). These reactions have been noted in both health care workers and people employed in factories that produce rubber products (17).

Currently, the diagnosis of latex allergy is primarily based on the clinical history. Patients should be questioned if they have ever noted erythema, pruritus, urticaria, or angioedema after contact with rubber products. Unexplained

episodes of urticaria and anaphylaxis should be scrutinized. Also, the work history may uncover potential occupational exposure to latex. In some patients, contact dermatitis may precede IgE-mediated reactions. *In vivo* and *in vitro* testing for the presence of latex-induced IgE antibodies has limited value. Skin prick tests (SPTs) using commercial latex reagents have been widely used in Europe and Canada. In the United States, there are no standardized, licensed latex extracts for diagnostic use. Once the diagnosis of latex allergy is established, avoidance is the only effective therapy. Natural rubber latex is ubiquitous, and avoidance can be challenging. Additional protective measures for individuals with known latex allergy include wearing a MedicAlert bracelet, having autoinjectable epinephrine available, and keeping a supply of nonlatex gloves for emergencies. Because there has been association between latex allergy and allergy to certain foods, latex-sensitive patients should be queried about reactions to bananas, avocado, kiwi fruit, chestnuts, and passion fruit, and advised to be cautious when ingesting them.

Prevention of latex allergy is the goal. When the Mayo Clinic changed to low-latex nonpowdered gloves, the incidence of latex sensitization decreased significantly (18). Dr. Baur and his colleagues reported reduction in latex aeroallergens after removal of powdered latex gloves from their hospital; other studies to address this strategy have also reported reduction in latex sensitization.

BLOOD PRODUCTS

Transfusions of blood products (e.g., red cells, white cells, platelets, fresh frozen plasma) may elicit serious reactions in 1% of cases (19). Anaphylactic shock occurs in 1:20,000 to 1:50,000. There are probably four different mechanisms that result in anaphylactic transfusion reactions: IgE-mediated against foreign protein, IgE-mediated against a hapten-self protein conjugate, complement activation with anaphylatoxin generation, and direct activation of mast cells. The most common manifestations of transfusion reactions are dyspnea, fever, hypotension, and urticaria (20).

Because they may have preexisting serum IgE or IgG antibodies to IgA, it has been recommended that IgA-deficient patients receive preparations from IgA-deficient donors; however, only a tiny minority of anaphylactic transfusion reactions are related to IgE or even IgG anti-IgA. Most patients with IgA deficiency can receive blood products without anaphylaxis in the absence of pretreatment. There is a practical issue of securing sufficient blood components for IgA-deficient patients if a strict policy were to be enforced. Although it has

been suggested that pretreatment with corticosteroids and antihistamines may be helpful in some cases, severe reactions may occur. Epinephrine should be readily available for treatment.

■ IMMUNE SERA THERAPY: HETEROLOGOUS AND HUMAN

Background

The two major allergic reactions that may follow an injection of heterologous antisera are anaphylaxis and serum sickness. Anaphylaxis is less common but is very likely to occur among patients who are atopic and have IgE antibodies directed against the corresponding animal dander, most commonly horse. For this reason, such individuals may react after the first injection of antisera. Serum sickness is more common and is dose related.

Current immunization procedures and the availability of human immune serum globulin (ISG) and specific immune serum globulin (SISG) preparations have reduced the need for heterologous antisera. However, equine antitoxins may still be required in the management of snakebite (pit vipers and coral snake), black widow spider bite, diphtheria, and botulism (21,22). Antilymphocyte globulin and ATG, prepared in horses and rabbits, have been used to provide immunosuppression for transplants and to treat aplastic anemia. Where available and appropriate, human ISG and SISG preparations should be used in preference to animal antisera. Although infrequent, anaphylaxis has followed the administration of human ISG preparations. Intramuscular ISG preparations contain high-molecular-weight IgG aggregates that are biologically active and may activate serum complement to produce anaphylatoxins. Anaphylaxis has also followed the administration of both intramuscular and intravenous (IV) human ISG among IgA-deficient patients who may produce IgE and IgG antibodies directed against IgA.

Tests before Heterologous Antisera Administration

Before administering heterologous antisera, skin testing, as indicated in the package insert, should be performed to determine whether there is the presence of IgE antibodies and thereby predict the likelihood of anaphylaxis. Most package inserts have suggested procedures. If not, SPT using antisera diluted 1:10 with normal saline, a histamine control, and a saline control are performed. If negative after 15 minutes, intradermal skin tests using 0.02 mL of a 1:100 dilution of antisera and a saline control are completed. If the history suggests a

previous reaction, or if the patient has atopic symptoms after exposure to the corresponding animal, begin intradermal testing using 0.02 mL of a 1:1,000 dilution. A negative skin test virtually excludes significant anaphylactic sensitivity, but some would recommend giving a test dose of 0.5 mL of undiluted antisera intravenously before proceeding with recommended doses. Although most studies report good predictive value of skin testing, some do not (23). It should be remembered that this approach does not exclude the possibility of a late reaction, notably serum sickness 8 to 12 days later.

Desensitization

When there is no alternative to the use of heterologous antisera, desensitization has been successful. The procedure is dangerous and may be more difficult to accomplish in patients who are allergic to the corresponding animal dander. There are several protocols recommended for desensitization. The package insert often recommends at least one such schedule. An IV infusion should be established in both arms. A conservative schedule begins with the subcutaneous administration of 0.1 mL of a 1:100 dilution in an extremity, where a tourniquet may be placed proximally if required. The dose is doubled every 15 minutes. If a reaction occurs, it is treated, and desensitization is resumed using one-tenth to one-half the dose provoking the reaction. After reaching 1 mL of the undiluted antiserum, the remainder may be given by slow IV infusion.

At times, more rapid delivery of the antisera may be required. In that case, IV infusions are also established in both arms, one to administer the antisera and the other for treatment of complications. Initiate a slow infusion of the antisera through one of the IV lines. If there is no reaction after 15 minutes, the infusion rate may be increased. If a reaction occurs, the antisera infusion is stopped and the reaction treated appropriately. After the reaction has been controlled, the slow infusion is reestablished. Most patients can be given 80 to 100 mL over 4 hours. If there is no reaction, it is possible to give that amount in the first hour. Other desensitization protocols for equine sera have been reported (24). After successful desensitization, it is possible that serum sickness will develop in 8 to 12 days. If the dose of antisera is in excess of 100 mL, virtually all patients will experience some degree of serum sickness. Treatment with corticosteroids is effective, the prognosis is excellent, and long-term complications are rare.

Immunoglobulin is often given to patients with humoral immune deficiencies. Adverse reactions are common, but generally not serious. Most can be prevented or treated by reducing the infusion rate or using medications, such as

nonsteroidal anti-inflammatory drugs, antihistamines, or corticosteroids (25). IgA deficiency increases the risk of some adverse reactions but is not a contraindication. Subcutaneous immunoglobulin is more slowly absorbed and associated with fewer adverse events than IV administration. Other human immunoglobulins, including ISGs, SISGs, and plasma concentrates, are generally well tolerated (26). However, serious reactions, including anaphylaxis, have been reported (27).

BIOLOGIC AGENTS

As is reviewed extensively in Chapter 1, the human immune system is regulated by a variety of proteins, including cytokines, chemokines, hormones, and colony-stimulating factors (CSFs). Many of those proteins, and their corresponding receptors, have been sequenced and cloned. In many cases, human recombinant proteins, antibodies against the proteins or their receptors have been produced for therapeutic purposes; it is hoped that these new therapeutic agents will favorably influence diseases characterized by neoplasia or inappropriate inflammation. These proteins have been collectively called "biologic response modifiers," "biologic agents," or "biologics."

Inasmuch as biologic agents are proteins, hypersensitivity reactions and other immunologic responses can be induced by biologic agents. There is research into pharmacogenomics and biomarkers predictive of adverse effects of biologics (28,29). For example, some genetic polymorphisms in the Fc γ-receptor may modulate the immune response to some biologics (30). To classify adverse events as a result of biologic agents, a five-category rubric for reactions, both immunologic and nonimmunologic, has been proposed by Pichler and Campi (31). Other classification systems have been reported (32,33). In the Pichler–Campi classification, type α reactions result in massive cytokine release, sometimes called "cytokine storm" or cytokine release syndrome; an example would be the severe, even fatal capillary leak syndrome that may occur with administration of a monoclonal antibody against CD3, a ubiquitous T-cell surface marker. Type β reactions are hypersensitivity reactions, which are the focus of this chapter; most hypersensitivity reactions are mediated by IgE, IgG, or T cells.

Type γ reactions result in immune imbalance, either immunodeficiency or autoimmunity; for example, antitumor necrosis factors (anti-TNFs) can impair the immune system enough to predispose to infections like tuberculosis, and they can also result in generation of antinuclear antibodies, occasionally inducing

clinically apparent lupus. Type δ reactions are due to cross-reactivity. For example, epidermal growth factor receptor (EGFR) is expressed on many types of carcinomas and is also found on normal skin. Although anti-EGFRs reduce carcinoma size, they also commonly cause an acneiform eruption that is believed to be caused by the action of anti-EGFRs on normal skin receptors. Finally, type ε reactions occur when a given molecule is unexpectedly found to participate in a different physiologic function. For instance, when CD40 inhibitors were administered, they caused thrombosis in a significant number of patients. It was then discovered that CD40 and CD40L are present on platelets.

Another adverse event that occurs with biologic agents that is not included in the Pichler–Campi classification is the development of neutralizing antibodies. Perhaps, in a future classification, it can be referred to as a type ζ reaction. Sometimes, the side effect is simply that the biologic agent is no longer effective, as occurs when antibodies to INFs develop and patients being treated for hepatitis C have relapses. Unfortunately, if the antibodies are very cross-reactive with endogenous protein, severe reactions can occur as has been reported in patients being treated with erythropoietin whose antibody development resulted in severe, red cell aplasia caused by neutralization of their own endogenously produced erythropoietin.

Depending upon the severity of the reaction and the necessity of the biologic, there are a number of graded dose protocols that have been published for readministration of a biologic after an α- or β-type reaction (33,34). Generally, the protocols start with one-hundredth of the target biologic concentration and one-tenth of the target rate; the dose is doubled every 15 minutes if tolerated. Some of those protocols are labeled as "desensitization," but that may not necessarily be the mechanism at work.

Monoclonal Antibodies

Clinical trials with monoclonal antibodies have reported their potential uses as diagnostic and therapeutic agents for malignant disease, inflammatory bowel disease, and several autoimmune diseases. However, various adverse events can make their administration difficult. Monoclonal antibodies have suffixes that indicate whether they are murine (-omab), chimeric (-iximab), humanized (-zumab), or fully human (-umab). Hypersensitivity reactions are most likely to occur with murine proteins and least likely to occur with fully humanized products. Hypersensitivity reactions may include fever, chills, rigors, diaphoresis, malaise, pruritus, urticaria, nausea, dyspnea, and hypotension.

Although rare, anaphylaxis has also been reported (33). Monoclonal antibodies may also cross-react with normal tissue, resulting in various adverse effects depending on the affected tissue (35). For example, both neuropathy and encephalopathy have been reported.

One study reported that an anti-CD20, rituximab, was well tolerated by patients with non-Hodgkin lymphoma (36). However, in one study of patients with a different disease, chronic lymphocytic leukemia, cytokine release syndrome, a type α reaction, was reported to occur in several patients after receiving rituximab (37). The elevated cytokine levels were associated with clinical symptoms, including fever, chills, nausea, vomiting, dyspnea, and hypotension. The severity and frequency of these events was associated with the number of circulating tumor cells at baseline.

TNF is a key cytokine in the inflammation of a variety of diseases, including inflammatory bowel disease, psoriasis, and rheumatoid arthritis. TNF antagonists include infliximab, adalimumab, and etanercept. Reports of significant type γ reactions, both immunodeficiency and autoimmunity, have been published relative to these agents (33). In addition, both IgE-mediated anaphylaxis and IgG-mediated serum sickness type β hypersensitivity reactions have been reported.

Polyclonal sheep anti-digoxin antibodies have proved useful when administered to patients with digoxin overdose. Unfortunately, significant hypersensitivity reactions, including severe anaphylaxis, have been described (38). Anti-CD3 monoclonal antibody has been reported to cause type α, cytokine release syndrome, reactions; patients may become resistant to treatment as a result of the development of neutralizing antibody (39).

As mentioned previously, EGFR antagonists are associated with significant type δ reactions, and, at the same time, have demonstrated activity against heretofore difficult-to-treat carcinomas, such as lung, colon, and pancreatic cancer. Agents include erlotinib, cetuximab, and panitumumab. A stepwise approach to characterizing and managing these adverse immunologic reactions has been developed by an international consensus (40). Because new biologic agents with promising therapeutic potential and adverse reaction profiles are identified, it will be key to have allergist-immunologists involved in the development of strategies to characterize and manage adverse reactions to clinically effective biologic agents (33).

The epidemiology of adverse reactions to monoclonal antibodies has not been well studied. In a 2016 Korean report, 19% of the total study population of 7,569

patients showed suspected hypersensitivity reactions (41).

Human Recombinant Proteins

Recombinant human granulocyte macrophage-CSF (GM-CSF) is used to accelerate myeloid recovery after bone marrow transplantation or high-dose chemotherapy. In a patient with pruritus, urticaria, and angioedema after GM-CSF administration, positive prick tests were reported with 100 and 250 µg/mL. There are other reports of anaphylaxis in the literature (42). There are also reports of localized reactions and generalized maculopapular eruptions. The immunopathogenesis of the latter reactions has not been well characterized. GM-CSF has also been reported to induce antibodies that neutralize the biologic activity of GM-CSF, thus compromising its therapeutic efficacy (43).

Hypersensitivity reactions, including anaphylaxis, have been reported with erythropoietin, and neutralizing antibodies have been reported. In one patient, antibody development was actually associated with red blood cell aplasia that resolved when erythropoietin was discontinued and the antibody titers declined (44). A rapid serologic method for detecting antirecombinant human erythropoietin antibodies has been published as a tool for the diagnosis of erythropoietin resistance. Antibody production against erythropoietin should be considered in the evaluation of patients whose anemia becomes refractory to erythropoietin therapy.

Recombinant interferon α (rIFN-α) has been reported to be a useful therapy in patients with mastocytosis, chronic myelogenous leukemia (CML), and chronic granulomatous disease (CGD). In some of these patients, development of antibody against rIFN-α has been reported (45). The prevalence varies from 1.2% to 20.2%, depending on the preparation. In some studies, the development of antibodies was associated with a relapse of disease, and it is presumed that the antibody was inactivating the rIFN-α. In the treatment of patients with CML, neutralizing antibody has also been associated with relapse. It has been reported that the epitopes, which are recognized by neutralizing antibody, are located in the N-terminal function domain of rIFN-α (46).

CGD has been reported to be treated safely and effectively with rIFN-α. However, high-avidity IFN-neutralizing antibodies have been reported in pharmacologically prepared human immunoglobulin. In a patient receiving rIFN-α for systemic mastocytosis, anti-IFN antibodies were reported. Cessation of the rIFN-α therapy resulted in a decline of antibody titer (47).

Other Recombinant Proteins

Hirudin is a thrombin inhibitor found in the salivary glands of leeches. In a trial of use of recombinant hirudin as an anticoagulant, an IgE-mediated hypersensitivity reaction was reported (48). Although tPA is generally not a cause of hypersensitivity reactions, a case of anaphylaxis temporally related to its administration has been reported (49); IgE antibodies directed against tPA have been detected in serum. In patients with cystic fibrosis treated with recombinant DNAase, a few patients developed antibody, but there have been no reports of anaphylaxis or other significant hypersensitivity reactions (50). In patients treated with humanized monoclonal antibody against IgE (omalizumab), patients have developed adverse effects, including the possibility of anaphylaxis that can be delayed (33).

Another area of study is whether biosimilar monoclonal antibodies are actually bioequivalent to the reference monoclonal antibody. There have been two reports showing similar safety and immunogenicity of biosimilar infliximab (51) and granulocyte CSF (52).

■ NANOMATERIALS

Nanomedicinal products (NMPs) such as liposomes or polymer conjugates can target specific tissues. Almost always, the NMPs will eventually travel to the immune system via phagocytosis (53). Adverse immune effects, including hypersensitivity, immunosuppression, and immune activation, have been reported (53,54). The aim of the ongoing investigation is to design NMBs with minimal immune effects.

■ VACCINES

As reviewed in the 2012 practice parameters (55), a variety of adverse reactions can result from vaccine administration: arthralgias from rubella vaccines, fever from pertussis vaccines, and fever with rash from live measles vaccine. A second risk of immunization is the possibility of reactions to vaccine components, such as egg, gelatin, latex, and neomycin. Another risk that occurs, for example, with frequent tetanus toxoid exposure, is the development of IgE antibodies with resultant anaphylaxis or urticaria. There have been reports of vaccine-associated dermatologic conditions, including lichen planus and Sweet syndrome (56). Exacerbation of atopic symptoms has also been reported (57). In a 2015 Australian report, vaccine anaphylaxis was rare, occurring at a rate of about 1 in 1,000,000. Epinephrine was administered in most cases, and no permanent

sequelae were noted (58).

The Vaccine Adverse Event Reporting System (VAERS) in the United States should receive reports of all serious vaccine events. In cases where the previous reaction was serious, IgG levels may be useful to determine whether there is still immunologic protection, obviating the need for subsequent doses (55).

Tetanus Toxoid

Although minor reactions, such as local swelling, are common after tetanus toxoid or diphtheria-tetanus toxoid vaccinations, true IgE-mediated reactions are rare. A number of case reports have been published, but surveys estimate the risk of a systemic reaction to be very small, 0.00001% (59). Because diphtheria toxoid is not available as a single agent, it is impossible to separate the true incidence of diphtheria-associated reactions from those caused by tetanus toxoid.

When it appears necessary to administer tetanus toxoid to a patient with a history of a previous adverse reaction, a skin test–graded challenge may be performed. One method is to begin with a SPT using undiluted toxoid. If negative, at 15-minute intervals, 0.02 mL of successive dilutions of toxoid 1:1,000 and 1:100 are injected intradermally. If the prick test was positive, begin with a 1:10,000 dilution. Subsequently, 0.02 and 0.20 mL of a 1:10 dilution are given subcutaneously. This may be followed by subcutaneous administration of 0.05, 0.10, 0.15, and 0.20 mL of full-strength toxoid. Some would prefer to wait for 24 hours after 0.10 mL is given to detect delayed reactivity. After that, the balance of full-strength material may be given for a final total dose of 0.50 mL.

Pertussis and Rubella

The Institute of Medicine analyzed adverse effects of pertussis and rubella vaccines (60). With cellular pertussis vaccines, reactions at the site are common, as is fever. Seizures occur in 1 in every 1,750 injections, as does the "collapse syndrome," hypotonic, hyporesponsive episodes. Reactions are much less common with acellular vaccines that are more commonly used in high-resource areas. Rubella vaccination results in arthritis and arthralgia in a significant percentage of adult and adolescent females. The incidence of arthralgia among children is very low.

Measles, Mumps, Rubella

Because the live attenuated virus used in the measles, mumps, rubella (MMR) vaccine is grown in cultured chick-embryo fibroblasts, concern has been raised

regarding its administration to egg-allergic children. The Advisory Committee on Immunization Practices no longer recommends skin testing or test dosing in egg-allergic subjects who are to receive MMR (61). It should be noted that hypersensitivity reactions to MMR vaccine have been described in children who tolerate eggs. There are reports that indicate that those reactions are due to another component, gelatin (62). In addition to causing anaphylaxis in patients receiving MMR, anaphylaxis caused by gelatin has been reported in patients receiving other vaccines, such as Japanese encephalitis vaccine (63).

Influenza and Yellow Fever Vaccine in Egg-Allergic Patients

Allergic reactions to influenza vaccine are rare, and the vaccine may be given safely to people who are able to tolerate eggs by ingestion, even if they demonstrate a positive skin test to egg protein (64). Anaphylaxis to influenza vaccine has been reported at a rate of 0.024:100,000.

Travelers to endemic areas may require immunization with yellow fever vaccine. Of the egg-based vaccines, yellow fever vaccine contains the most egg protein. Yellow fever vaccine also contains gelatin. In a review of 5,236,820 vaccinations, it was estimated that the risk of anaphylaxis was about 1 in 131,000 (65). The Centers for Disease Control and Prevention (CDC) lists egg hypersensitivity as one of the reasons that an individual should not receive yellow fever vaccine. It is suggested that the individual obtain a waiver letter from a consular or an embassy official (66). For patients with a history of egg allergy, skin testing with the appropriate vaccine is a reliable method to identify the patients at risk. A prick test is performed with a 1:10 dilution of the vaccine in normal saline and a normal saline control. If negative or equivocal, an intradermal skin test using 0.02 mL of a 1:100 dilution of the vaccine and a saline control are performed. If negative, the vaccine may be administered in a routine manner.

After a positive skin test to the vaccine, if it is considered essential, administer 0.05 mL of a 1:100 dilution intramuscularly and, at 15- to 20-minute intervals, give 0.05 mL of a 1:10 dilution, 0.05 mL of undiluted vaccine, followed by 0.10, 0.15, and 0.20 mL of undiluted vaccine for a total dose of 0.50 mL. Using this procedure, patients develop adequate protective antibody titers.

Other Vaccines

Both typhoid and paratyphoid vaccines have been reported to cause anaphylaxis (67). In a study of 14,249 marines who received Japanese encephalitis vaccine,

the reaction rate was 0.00267% (68). The reactions were primarily urticaria, angioedema, and pruritus. In a study of 1,198,751 individuals who received meningococcal vaccine, the rate of anaphylaxis was reported as 0.1 in 100,000, a very rare event (69). Because varicella vaccine contains neomycin, individuals with neomycin hypersensitivity would be at potential risk of an allergic reaction (70). There are case reports of anaphylactic episodes after hepatitis B vaccine (71). In addition, hypersensitivity reactions may occur because of a variety of vaccine components (55).

For the most current information on adverse reactions to vaccines, the CDC website is very useful (72), as are the 2012 practice parameters (55). In addition, if an adverse effect occurs after a patient receives a vaccine, the CDC has established a VAERS that allows for reporting by fax, mail, or online (73).

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Food Allergies

EDWIN KIM AND WESLEY BURKS

INTRODUCTION

Symptoms related to the ingestion of foods occur commonly and are often casually referred to as food allergies. These adverse food reactions occur by a variety of mechanisms and result in varying clinical presentations. In an attempt to standardize nomenclature in the scientific literature, the National Institutes of Health defined adverse food reactions as any untoward reaction to a food or food additive following ingestion (1). These reactions are further subdivided into food allergy and food intolerance. Food allergy describes any adverse food reaction caused by an immunologic mechanism. Food allergies can be immunoglobin E (IgE)-mediated or non–IgE-mediated and are the focus of this chapter. In contrast, food intolerance describes an adverse food reaction caused by a nonimmunologic mechanism. As examples, food intolerances may be the result of pharmacologic properties of the food (e.g., caffeine), toxins in the food (e.g., histamine in scombroid fish poisoning; bacterial food poisoning), foods that exacerbate reflux (peppermint, spicy or acidic food), or metabolic deficiencies (lactase deficiency and pancreatic insufficiency) (Table 18.1).

This chapter summarizes several key areas related to food allergy, including epidemiology, mucosal immunity and the development of food allergy, common food allergens, and the clinical presentation of IgE- and non–IgE-mediated food reactions. Other areas that are reviewed include the diagnosis and management of food allergy, the natural history of food allergy, and exciting new developments in food allergy prevention and treatment.

EPIDEMIOLOGY

The true incidence and prevalence of food allergy has been difficult to accurately determine. Recent epidemiologic studies have suggested that nearly 15 million Americans are afflicted with food allergy and that children are more affected than adults (2). In Europe, one study utilizing a randomized telephone survey and standardized questionnaire reported an approximate measure for food allergy prevalence to be 3.75%, with the most affected age group being 2- to 3-year-olds

(3). Furthermore, studies have suggested a significant increase in the prevalence of food allergy over the past 20 years, paralleling the increase in asthma and other atopic diseases (4).

TABLE 18.1 FOOD ALLERGY: DIFFERENTIAL DIAGNOSIS

1. Gastrointestinal disorders

    • Structural abnormalities
    • Enzyme deficiencies
    • Cystic fibrosis

2. Contaminants and additives

    • Flavorings, dyes, preservatives, contaminants
    • Infectious organisms
    • Seafood-associated disorders

3. Pharmacologic contaminants

    • Caffeine, histamine, tyramine

4. Psychologic reactions

    • Bulimia, anorexia, factitious

Unfortunately, the overall prevalence of food allergy has traditionally been overestimated. In one investigation, 28% of mothers perceived their children to have had at least one adverse reaction to food (5), but only 8% or one-third of these children had reactions confirmed by double-blind, placebo-controlled food challenges (DBPCFC). A study of a birth cohort from the Isle of Wright (UK) showed a cumulative incidence of parentally reported food allergy of 25.8% (95% confidence interval [CI], 23.1% to 28.7%) by 12 months; however, the cumulative incidence of food allergy based on open food challenges was found to be 4% (95% CI, 2.9% to 5.5%) (6). By 3 years of age, 33.7% of families in this cohort reported a food allergy compared to an actual incidence of food

allergy based on food challenges and a good clinical history of 5% to 6% (7). A recent meta-analysis reviewed the prevalence of food allergy according to the method of assessment used (8). The prevalence of self-reported food allergy was very high, 3% to 35% for any food. The heterogeneity in the prevalence of food allergy could have been a result of differences in study design or methodology, or differences among populations.

Within the past few years, specific investigations have examined the prevalence rates of allergy to specific foods, such as peanuts and seafood, which typically can be severe, lifelong, and potentially fatal. First, in North America and the United Kingdom, the prevalence rates of peanut allergy among school-aged children have been found to be in the excess of 1% (9). Second, physician-diagnosed and/or convincing seafood allergy has been reported by 2.3% of the general population, or approximately 6.6 million Americans (10).

The epidemiology of food allergy can certainly be influenced by the atopic history of the patient (Table 18.2). For example, the prevalence of food allergy appears to be approximately 30% in children with moderate/severe refractory atopic dermatitis (11). An Australian investigation determined the relative risk of an infant with atopic dermatitis having an IgE-mediated food allergy was 5.9% for the most severely affected group (12).

MUCOSAL IMMUNITY AND PATHOPHYSIOLOGY

Mucosal Barrier

The main function of the gastrointestinal tract is to process ingested food into a form that can be absorbed and utilized for energy and cell growth. This process requires that the intestinal immune system be capable of discriminating between harmful and harmless foreign proteins (13). Both nonimmunologic and immunologic mechanisms help to block harmful foreign antigens (bacteria, viruses, parasites, and food proteins) from entering the interior of the body, thus forming the gastrointestinal "mucosal barrier." The developmental immaturity of these mechanisms in infants reduces the efficiency of the infant mucosal barrier, and likely plays a major role in the increased prevalence of gastrointestinal infections and food allergy seen in the first few years of life. The relatively low concentrations of (secretory) S-IgA in the infant's intestine and the relatively large quantities of ingested proteins place a significant burden on the immature gut-associated immune system (GALT).

The GALT must mount a significant response against potentially harmful

foreign substances and pathogenic organisms, but must remain unresponsive to enormous quantities of nutrient antigens and about 10^{14} commensal organisms forming the normal gut flora. The GALT is comprised of four distinct lymphoid compartments: (a) Peyer patches and the appendix (aggregates of lymphoid follicles throughout the intestinal mucosa), (b) lamina propria lymphocytes and plasma cells, (c) intraepithelial lymphocytes interdigitated between enterocytes, and (d) mesenteric lymph nodes (13).

S-IgA, a dimeric form of IgA that is found in intestinal secretions, does not activate complement or bind to Fc receptors and, therefore, does not induce inflammatory responses. S-IgA antibodies are directed against bacterial or viral surface molecules that can prevent their binding to the epithelium and/or facilitate agglutinating pathogens, resulting in complexes that become trapped in the mucus barrier and pass out in the stool (14). Despite the evolution of this well-developed barrier system, about 2% of ingested food antigens are absorbed and transported throughout the body in an "immunologically" intact form, even through the mature gut (15).

TABLE 18.2 FOOD ALLERGY PREVALENCE IN SPECIFIC DISORDERS

DISORDER	FOOD ALLERGY PREVALENCE
Anaphylaxis	35%
Atopic dermatitis	37% in children (rare in adults)
Urticaria	20% in acute cases (rare in chronic)
Asthma	5%–6% in children with asthma
Oral allergy syndrome	25%–75% in pollen allergy
Chronic rhinitis	Rare

Oral Tolerance Induction

Intact food antigens penetrate the gastrointestinal tract and enter the circulation in both normal children and adults (16,17). However, these intact proteins are usually poor immunogens and do not normally cause clinical symptoms. This phenomenon is termed oral tolerance and is defined as an unresponsiveness of the immune system to specific antigens that is induced by the prior feeding of the antigen (13). An interplay between the natural gut flora and immunologic mechanisms is thought to be responsible for the development of oral tolerance. Commensal gut flora take residence in the gastrointestinal tract within 24 hours of birth at a concentration that has been estimated to be between 10^{12} and 10^{14} bacteria per gram of colon tissue (18). The impact of gut flora on oral tolerance is supported by the finding that mice raised in germ-free environments following birth are unable to develop tolerance to orally administered ovalbumin (19). The unresponsiveness of T cells to ingested food proteins may be the result of three different mechanisms: induction of regulatory T-cells, T-cell clonal deletion, or T-cell anergy.

Normal Immune Response to Ingested Antigens

The presentation of food antigens on antigen presenting cells as with other antigens leads to an immune response and the development of antibodies. As a result, low concentrations of detectable serum IgG, IgM, and IgA food-specific antibodies are commonly found in normal individuals (20). In general, the younger an infant when a food antigen is introduced into the diet, the more pronounced the antibody response (21). As an example, following the introduction of cow's milk, serum milk protein–specific IgG antibodies rise over the first month, achieving peak antibody levels after several months, and then generally decline, even though cow's milk proteins continue to be ingested (22). Individuals with various inflammatory gastrointestinal disorders (e.g., celiac disease, food allergy, inflammatory bowel disease) frequently have high levels of food-specific IgG and IgM antibodies. It is important to recognize that the presence of these antibodies alone does not indicate that the patient is allergic to these foods (23). On the contrary, the increased levels of these non–IgE food-specific antibodies appear to be secondary to increased gastrointestinal permeability to food antigens and simply reflect dietary intake.

FOOD ALLERGENS

Sensitization to food allergens occurs primarily after direct exposure to the allergen in the gastrointestinal tract or, possibly, through the skin. This method of sensitization is referred to as "traditional" or class 1 food allergy.

Sensitization to foods allergens can also occur after exposure to related but distinct inhalant allergens which is termed class 2 food allergy (24). The major food allergens that have been identified in class 1 allergy are water-soluble glycoproteins that have molecular weights ranging from 10 to 70 kD and are stable to treatment with heat, acid, and proteases (25) (Table 18.3). In contrast, there are no consistent physicochemical properties common to the class 2 food allergens which are homologous to pollen allergens and cause pollen food allergy syndrome (PFAS), also called oral allergy syndrome. The majority of these generally plant-derived proteins are highly heat labile and difficult to extract. A number of the class 1 and 2 food allergens have been identified, cloned, sequenced, and expressed as recombinant proteins. Many of the class 2 plant-related allergens are homologous to pathogen-related proteins (PRs), which are expressed by the plant in response to infections or other stress factors, or comprise seed storage proteins, profilins, peroxidases, or protease inhibitors common to many plants (26). Examples of common class 1 and class 2 allergens are reviewed below.

TABLE 18.3 FOOD ALLERGEN CHARACTERISTICS

1. Proteins (carbohydrate, not fat)

   - 10–70 kD Glycoproteins
   - Heat resistant, acid stable

2. Major allergenic foods (>85% of allergy)

   - Children: cow's milk, eggs, peanuts, soy, and wheat
   - Adults: peanuts, tree nuts, shellfish, and fish

3. Single food > many food allergies

4. Characterization of epitopes underway

   - Linear versus conformational epitopes
   - B-cell versus T-cell epitopes

Cow's Milk

Allergy to cow's milk is the most common food allergy in young children with IgE-mediated cow's milk allergy affecting 2.5% of children less than 2 years of age (1). Cow's milk contains at least 20 protein components, which may lead to antibody production in humans (27). The milk protein fractions are subdivided into casein and whey proteins (76% to 86%, respectively) with evidence demonstrating the casein proteins to be the more allergenic fraction (28). The casein fraction is precipitated from skim milk by acid at pH 4.6 and is comprised of four basic caseins (α_{s1}, α_{s2}, β, and κ comprising 32%, 10%, 28%, and 10% of the total milk protein, respectively). The whey fraction consists of β-lactoglobulin, α-lactalbumin, bovine immunoglobulins, bovine serum albumin, and minute quantities of various proteins (e.g., lactoferrin, transferrin, lipases, esterases). Extensive heating is capable of destroying several of the whey proteins. However, routine pasteurization is not sufficient to denature these proteins and paradoxically has been reported to increase the allergenicity of some milk proteins, such as β-lactoglobulin (29). Sequential (linear) allergenic (IgE) epitopes have been mapped on the caseins as well as on β-lactoglobulin and α-lactalbumin, and have been correlated with the persistence of cow's milk allergy (30–32).

IgE-immunoblotting techniques have demonstrated cross-reactivity among milk proteins in cows, goats, and sheep owing to the high degree of homology among these proteins. Oral challenge studies in cow's milk-allergic children indicated that at least 90% of cow's milk-allergic children will react to goat's milk (33). Interestingly, about 10% of milk-allergic children will react to beef, with a slightly higher number reacting to rare beef (34).

Hen's Egg

Hen's egg allergy is another common IgE-mediated food allergy in children. The egg white has been shown to be more strongly allergenic than the yolk and contains 23 different glycoproteins with ovomucoid, ovalbumin, and ovotransferin being identified as the major allergens (35,36). Although ovalbumin comprises the majority of the protein in egg white, ovomucoid has been shown to be the dominant allergen (37). Ovomucoid (*Gal d 1*) is comprised of 186 amino acids arranged in three tandem domains, a set tertiary structure, and six sequential (linear) IgE-binding sites. Blinded oral food challenges (OFCs) with ovomucoid-depleted egg white have demonstrated that ovomucoid is responsible for clinical reactivity in the vast majority of egg-allergic children

(38). Interestingly, it seems that the majority of egg-allergic children are able to ingest small amounts of egg protein in extensively heated (baked) products (e.g., breads, cakes, and cookies) (39). The mechanisms of this tolerance are hypothesized to include the destruction of heat-labile conformational epitopes and a food matrix effect, resulting in decreased availability of the protein to the immune system (40).

Peanut

The peanut, a member of the legume family, has become one of the most common food allergens in industrialized societies with recent data suggesting a prevalence that is greater than 1% in some countries (1). Peanut proteins have been traditionally classified as albumins (water-soluble) and globulins (saline-solution soluble), the latter of which is further subdivided into arachin and conarachin fractions (36). Three proteins with molecular weights of 63.5 kD (*Ara h 1*) (41), 17 kD (*Ara h 2*) (42), and 64 kD (*Ara h 3*) (43) have been identified as major allergens. *Ara h 1* belongs to the vicilin family of seed storage proteins, *Ara h 2* is a member of the conglutin family of storage proteins (44), and *Ara h 3* is a member of the glycinin family of storage of proteins (43). *Ara h 4-8* have also been identified (45). *Ara h 5* is a profilin, whereas *Ara h 4* appears to be an isoform of *Ara h 3*, and *Ara h 6* and *7* appear to be isoforms of *Ara h 2*. *Ara h 8* is a member of the pathogenesis-related PR-10 family and is primarily involved in PFAS, as described below (46). In contrast to cow's milk and hen's egg, standard cooking and processing does not affect the allergenicity of peanut protein; however, the significant levels of heating, pressurization, and refinement involved in the manufacturing of peanut oil is thought to result in minimal levels of intact protein. This is supported by a study where refined peanut oil was found to be safe in all 60 peanut-allergic individuals, whereas pressed (or extruded) oils were found to retain some of their allergenicity (47).

Tree Nuts

Tree nut allergies affect about 0.6% of the American population (48). In a national registry of peanut and tree nut allergic individuals, walnuts were the tree nut provoking the most allergic reactions (34%), followed by cashews (20%), almonds (15%), pecans (9%), and pistachios (7%). Hazelnuts, Brazil nuts, pine nuts, and macadamia nuts account for less than 5% of all tree nut allergies. Skin testing has revealed extensive immunologic cross-reactivity among tree nuts; however, too few patients have been systematically challenged to the various tree nuts to determine the true extent of clinical cross-reactivity. Surveys have

suggested that up to 35% to 50% of peanut-allergic patients may also be reactive to at least one tree nut (49,50). Although empiric avoidance of all tree nuts is not necessarily recommended in peanut-allergic patients, discussion with an allergist regarding the introduction of tree nuts would be warranted.

Seed Proteins

Compelling evidence exists that sesame seed allergy is becoming a serious public health problem in many countries around the globe (51,52). Sesame allergy has been identified mainly in populations where sesame is widely consumed, such as Israel, Asia, Australia, and Italy; however, sesame allergy is becoming more commonly recognized in the United Kingdom and United States as well (52–54). Sesame allergy is often associated with systemic anaphylaxis similar to peanut and tree nut allergies (55), and sesame allergy is rarely outgrown.

Soybean

Soybean is another member of the legume family that provokes a significant number of hypersensitivity reactions, predominantly in infants and young children. Because soybeans provide an inexpensive source of high-quality protein, soybean protein is used in many commercial foods. Approximately 10% of the seed proteins are water-soluble albumins, and the remainder are salt-soluble globulins. Four major protein fractions have been separated by ultracentrifugation: 2S (contained in whey fraction), 7S (50% β-conglycinin), 11S (glycinin), and 15S (aggregated glycinin). A number of soy proteins have been isolated and characterized, particularly a 34-kD thiol protease–like protein (*Gly m Bd 30K*). Interestingly, the allergenic epitopes on glycinin G1 acidic chain are homologous to IgE-binding epitopes on peanut *Ara h 3* (56). Similar to highly refined peanut oil, refined soy oil has not been found to provoke clinical reactions in soy-allergic individuals (57).

Wheat

Wheat (spelt) and other cereal grains share a number of homologous proteins and are implicated in food-allergic reactions in children. It has been suggested that the globulin and glutenin fractions are the major allergenic fractions in antibody-mediated reactions, whereas the gliadins have been implicated in celiac disease and albumins in Baker's asthma (58). More recent studies have suggested that the water-insoluble gliadin fraction may also be important in clinical reactivity to wheat, especially in cases of food-associated exercise-induced anaphylaxis

(59–61). Nonspecific binding to lectin fractions has been noted with each grain, and extensive immunologic cross-reactivity has been reported among the cereals which were corroborated with skin-prick testing. In addition, homologies to allergenic proteins in grass pollens has accounted for a large number of clinically irrelevant positive skin tests to wheat and other cereal grains.

Fish

Fish are one of the most common causes of food-allergic reactions in adults, and a common cause in children as well (8,62). The major allergen in cod, *Gad c 1*, is a parvalbumin that has been isolated from the myogen fraction of the white meat. It is heat stable and resistant to proteolytic digestion, has a molecular weight of 12 kD, an isoelectric point of 4.75, and is composed of 113 amino acids (63). The three-dimensional structure of *Gad c 1* has been defined and shown to be arranged in three domains, two of which bind calcium (64). The fish protein fraction(s) responsible for clinical symptoms in some patients may be susceptible to manipulation (e.g., heating, lyophilization), because reactions have been reported during open feedings of fresh fish in approximately 20% of those with negative DBPCFCs utilizing lyophilized fish (65). Furthermore, it was found that most patients allergic to fresh cooked salmon or tuna could ingest canned salmon or tuna without difficulty, indicating that preparation led to destruction of the major allergens. It is noteworthy that different from the other common food allergens, allergic reactions have been reported following exposure to airborne fish allergen emitted during cooking (64).

Shellfish

Shellfish allergens are considered a major cause of food-allergic reactions in adults, affecting up to 2.3% of the US adult population (8). This group consists of a wide variety of mollusks (snails, mussels, oysters, scallops, clams, squid, and octopus) and crustacea (lobsters, crabs, prawns, and shrimp). Shrimp allergens have been most extensively studied. Tropomyosin, a protein found both in muscle and elsewhere, has been identified as the major allergen in shrimp (66). Considerable cross-reactivity among crustacea has been demonstrated by skin test and *in vitro* IgE analyses (67). In particular, invertebrate tropomyosins are highly homologous and tend to be allergenic as has been seen with crustaceans (e.g., shrimp, crab, crawfish, and lobster), arachnids (house dust mites), insects (cockroaches), and mollusks (squid and snails) (68). On the other hand, vertebrate tropomyosins have not been commonly associated with allergy.

Pathogenesis-Related Proteins

PRs have been shown to comprise a large number of class 2 allergenic proteins found in various vegetables and fruits (Table 18.4) (24,69,70). These proteins are induced when the plant is wounded or are exposed to certain environmental stresses, such as drought and heat. PRs have been classified into 14 families, although six PR families account for the majority of cross-reactivity among plant proteins. Two families of chitinases that are similar to the latex allergen, *Hev b 6.02*, have been identified as allergens in a number of vegetables: PR-3 type proteins are found in chestnut and avocado (*Pers a 1*), whereas PR-4 type proteins are wound-induced proteins found in tomato and potato (*Win 1* and *Win 2* proteins). PR-5 type thaumatin-like proteins have been identified as cross-reacting proteins found in apples (*Mal d 2*) and cherry (*Pru av 2*). The PR-10 type proteins are homologous to the major birch pollen allergen, *Bet v* 1, and are a major cause of PFAS. These proteins account for cross-reactivity between birch pollen and fruits of the Rosaceae species: apple (*Mal d 1*), cherry (*Pru av 1*), apricot (*Pru ar 1*), pear (*Pyr c 1*); or vegetables of the Apiaceae species: carrot (*Dau c 1*), celery (*Api g 1*), and parsley (*pcPR 1* and 2); and hazelnut (*Cor a 1*). Cross-reactivity has also been seen with peanut (*Ara h 8*) (46). The lipid transfer proteins (LTPs), or PR-14 type proteins, form a family of 9 kD proteins distributed widely throughout the plant kingdom. LTPs have been identified as major allergenic proteins in Prunoideae species, such as peach (*Pru p 1* in peach skin and *Pru p 3* in the fruit), apple (*Mal d 3*), apricot, plum, and cherries. *Gly m 1*, a major allergen in soybean, has also been found to be an LTP.

Profilin

Profilin is an actin-binding protein that was first identified in birch pollen (*Bet v 2*) and is now recognized as an allergenic protein in a number of fruits and vegetables (24). Profilins are responsible for PFAS to apple (*Mal d 4*), pear (*Pyr c 4*), cherry (*Pru av 4*), celery (*Api g 4*), and potato in birch pollen–allergic patients, and are also responsible for the celery-mugwort-spice syndrome. Profilins have also been identified in tomato (*Lyc e 1*), peanut (*Ara h 5*), and soybean (*Gly m 3*), but whether these proteins cause allergic reactions remains to be established.

TABLE 18.4 **PATHOGENESIS-RELATED PROTEINS**

GROUP	PROTEIN CLASS	ALLERGEN SOURCE/ALLERGEN

PR-2	β-1,3 glucanases	Fruits and vegetables
PR-3	Class 1 chitinases	Avocado (*Pers a 1*), chestnut, and banana
PR-4	Chitinases	Tomato, potato (*Win 1* and *Win 2* proteins), turnip, and elderberry
PR-5	Thaumatin-like	Cherry (*Pru av 2*), apple (*Mal d 2*), bell pepper
PR-10	*Bet v 1* homologues	Apple (*Mal d 1*), cherry (*Pru av 1*), pear (*Pyr c 1*), celery (*Api g 1*), carrot (*Dau c 1*), potato, apricot (*Pru ar 1*), parsley, hazelnut (*Cor a 1*)
PR-14	Lipid transfer proteins	Peach skin (*Pru p 1*), peach pulp (*Pru p 3*), apple (*Mal d 3*), cherry (*Pru av 3*), apricot, plum, almond, soy (*Gly m 1*), barley

PR, pathogen-related protein.

■ IMMUNOGLOBIN E–MEDIATED FOOD REACTIONS

Immune responses mediated by specific IgE antibodies to food allergens are the most widely recognized mechanism for food-induced allergy symptoms (1). Atopic patients produce IgE antibodies to specific epitopes in the food allergen. These antibodies bind to high-affinity IgE receptors on basophils and tissue mast cells throughout the body. When antigen binds to multiple adjacent IgE antibodies on a mast cell or basophil, these cells become activated, degranulate, and release preformed mediators such as histamine and *de novo* synthesized mediators such as leukotrienes and prostaglandins. These mediators are responsible for the immediate allergic reaction and the clinical symptoms observed. Mast cell–derived mediators can also cause endothelial cells to increase expression of adhesion molecules for eosinophils, monocytes, and lymphocytes. These cells are recruited to the area and are responsible for the late-phase allergic response that is driven by the release of various cytokines and inflammatory mediators. The following section reviews the specific clinical manifestations of IgE-mediated food reactions.

Cutaneous Manifestations

Cutaneous manifestations are the most common clinical symptoms of food allergy (71). Cutaneous symptoms may present in isolation or as part of a systemic reaction with signs and symptoms from other organ systems, such as the gastrointestinal and respiratory systems (72). These cutaneous symptoms range from acute urticaria or angioedema to a morbilliform pruritic dermatitis. Urticaria can be elicited in approximately 12% of food challenges, and overall, the incidence of acute food-dependent urticaria is about 1% to 2% (72). However, it is important to note that chronic urticaria lasting more than 6 weeks is almost never caused by food allergy (73). Contact dermatitis has also been reported to various foods (74). True allergic contact dermatitis can proceed to a systemic reaction; therefore, a thorough diagnostic workup to rule out involvement of the immune system is important.

In children with atopic dermatitis, food allergies have been confirmed by DBPCFC in about one-third of the children (75,76). In one study of 210 children evaluated and followed to determine a relationship between food allergy and exacerbations of their atopic dermatitis, 62% of children had a reaction to at least one food. Of all reactions that occurred within 2 hours of a DBPCFC, 75% were cutaneous (77). Cutaneous manifestations predominantly involved erythema and pruritus, leading to scratching and exacerbation of the atopic dermatitis. Sampson and Broadbent reported an increase in histamine releasabililty in patients with atopic dermatitis who repeatedly ingested a known food allergen (78). This was probably due to the stimulation of mononuclear cells to secrete histamine-releasing factors, some of which interact with IgE molecules bound to the surface of basophils.

Gastrointestinal Manifestations

Gastrointestinal symptoms are the second most frequently observed manifestation of food allergy. Clinical presentations include nausea, vomiting, diarrhea, as well as abdominal pain and cramping. As with cutaneous manifestations, gastrointestinal symptoms may occur alone or in combination with symptoms from other organ systems. There is considerable evidence that many of these symptoms result from the activation of mast cells (79). Allergic eosinophilic gastroenteropathies represent a different class of immune-mediated food allergy and likely involve a combination of IgE- and non–IgE-mediated mechanisms; eosinophilic gastrointestinal disease is covered in Chapter 40.

Respiratory Manifestations

Respiratory symptoms are not as common in food allergy as cutaneous or gastrointestinal symptoms, but they remain critically important because they include some of the life-threatening manifestations of food allergy (71,80,81). Respiratory manifestations may include benign symptoms, such as sneezing, rhinorrhea, and ocular; otic; and palatal pruritus. However, they also include potentially life-threatening bronchospasm and laryngeal edema. Isolated airway symptoms as a manifestation of food allergy are rare but when present, can be associated with poor outcomes (82). Respiratory symptoms present more commonly as part of a broader systemic reaction. Wheezing, throat tightness, and nasal congestion were reported in 42% and 56% of respondents as part of their initial reactions to peanuts and tree nuts, respectively (54), and the presence of asthma was a risk factor for these patients to have more severe reactions (33% versus 21%; P < 0.0001). Furthermore, respiratory symptoms, including shortness of breath and throat tightness, were reported by more than 50% of patients with fish or shellfish allergy in a recent published survey (8).

Asthma Induced by Food Allergens

As described earlier, symptoms commonly associated with asthma, such as coughing, wheezing, and shortness of breath, can present as part of a systemic allergic reaction. However, the association of food allergens with the exacerbation of asthma, independent of systemic allergic reactions, has also been studied (83–85). Patients with food allergy and asthma were generally younger and had a past medical history of atopic dermatitis. Cow's milk and hen's egg allergy in particular were found to induce asthma exacerbations in children, especially those with atopic dermatitis (86–88).

Airway Hyperresponsiveness Induced by Food Allergy

It has been hypothesized that the chronic ingestion of a food to which the patient is allergic could result in increased airway hyperreactivity despite the absence of acute symptoms following ingestion (89). Significant increases in airway hyperreactivity, demonstrated with methacholine inhalation challenges, were documented several hours after positive food challenges in patients who experienced adverse chest symptoms during these food challenges. This investigation suggested that food-induced allergic reactions may increase airway reactivity in a subset of patients with moderate-to-severe asthma. However, this finding has been controversial because a different investigation concluded that food allergy was an unlikely cause of increased airway reactivity in adult

patients (90).

Occupational Asthma from Food Allergens

There have been several published reports of occupational asthma following the inhalation of relevant food allergens. These reactions are most likely the result of IgE-mediated food reactions that result from inhalation of aerosolized antigens, usually in an occupational setting. Although the resultant symptoms are the same as respiratory symptoms seen with aeroallergens (i.e., rhinoconjunctivitis and asthma), asthma is the most prominent symptom. Patients typically have IgE antibody to the food as demonstrated by skin tests or immunoassay.

A particular type of occupational asthma called Baker's asthma is caused by occupational exposure to airborne cereal grain dust that results in chronic asthma (91). A significant percentage of bakers develop occupational asthma and chronic obstructive bronchitis. There was a positive methacholine test in 33% of bakers with atopic status, compared to 6.1% ($P < 0.01$) of nonatopic bakers (92). Occupational asthma is discussed in additional detail in Chapter 25.

Anaphylaxis

Food is the most common cause of outpatient anaphylaxis, but the actual prevalence of food-induced anaphylaxis, an underrecognized and undertreated medical emergency, is not known (93–95). Food allergens account for up to 30% of fatal cases of anaphylaxis; one-third of cases occur at home, 25% in restaurants, and 15% at school or work. Reactions to peanuts and tree nuts accounted for 94% of fatalities (93). The most commonly implicated foods responsible for food-induced anaphylaxis include peanuts, tree nuts, fish, and shellfish. More recently, allergy to sesame seeds has also been identified as a cause of food-induced anaphylaxis (55).

Symptoms of food-induced anaphylaxis can vary widely but often include pruritus in the oropharynx, angioedema (e.g., laryngeal edema), stridor, cough, dyspnea, wheezing, and dysphonia. In a survey of six fatal and seven near-fatal anaphylactic reactions following food ingestion, all patients had asthma and respiratory symptoms as part of their clinical presentation (71). As described earlier, the foods responsible for these serious reactions were peanuts, tree nuts, hen's egg, and cow's milk. Another report summarized acute allergic reactions to peanuts and/or tree nuts in 122 atopic children. In the group, 52% had lower respiratory tract symptoms as part of their overall reactions supporting the key role of respiratory symptoms in anaphylaxis (50).

In summary, the presence of asthma and a short list of common food allergens are significant risk factors for serious and even fatal cases of food-induced anaphylaxis (90). Common themes associated with fatal food anaphylaxis include: (a) reactions resulting from peanut or tree nut ingestion, (b) teenage or young adult age, (c) a known history of asthma, and perhaps most importantly, (d) the failure to promptly administer epinephrine. Cutaneous symptoms are very common, appearing in more than 90% of cases (93,96,97); however, respiratory symptoms are most strongly associated with severe allergic reactions and anaphylaxis.

Food-Related Exercise-Induced Anaphylaxis

Although anaphylaxis is a well-described consequence of food allergy, the potential role of exercise in food-associated anaphylaxis is less clear. Anaphylaxis induced solely by exercise is a unique syndrome characterized by generalized body warmth, erythema, and pruritus, which can progress to fulminant anaphylaxis, including confluent urticaria, laryngeal edema, bronchospasm, gastrointestinal symptoms, hypotension, and even vascular collapse (98). A subset of these patients have symptoms only if exercise is performed within 2 to 6 hours of food ingestion (99), a disease termed food-related exercise-induced anaphylaxis. With food alone or exercise alone, there is no anaphylaxis; however, it is the combination of both that leads to symptoms (99,100). For some patients, this food-related exercise-induced anaphylaxis may occur with any food ingestion followed by exercise (99,100). Others have exercise-induced anaphylaxis only associated with the ingestion of specific foods, such as wheat (101), celery (99), or shellfish (94,102). Both high- and low-aerobic sports and physical activities have been associated with food-related exercise-induced anaphylaxis. Reports of fatalities have been rare and restricted to adults. These patients have positive skin tests to the foods confirming the presence of food-specific IgE, yet they have no allergic reactions unless ingestion is followed by or preceded by rigorous exercise (99,102). For all food-related exercise-induced anaphylaxis, episodes are prevented with avoidance of food ingestion 4 to 6 hours prior to or following exercise (100). Like other forms of anaphylaxis, it is thought to be mediated by mast cell degranulation, (98) but the role of exercise is unclear with theories suggesting increased permeability of the gut to food allergens, increased intestinal osmolality enhancing mast cell degranulation, and blood flow redistribution enabling transport of allergen to effector cells as possible mechanisms (101). Other aspects of anaphylaxis are covered in more detail in Chapter 14.

Pollen Food Allergy Syndrome or Oral Allergy Syndrome

As described earlier, certain patients can develop sensitization to food allergens as a consequence of exposure to inhalant allergens through the respiratory tract that is termed class 2 food allergy. Patients allergic to certain airborne pollens can display adverse reactions on the ingestion of plant-derived foods as a result of IgE cross-reactive structures shared by pollen and food allergen sources. This clinical entity was formally known as oral allergy syndrome but has been renamed pollen food allergy syndrome (PFAS). PFAS is considered to be a form of contact urticaria with symptoms resulting from interaction of the food allergen with the oral mucosa (103,104). Symptoms include pruritus with or without angioedema of the lips, tongue, palate, and posterior oropharynx. Shared allergen sensitivities have been reported between ragweed and the gourd family (watermelon, cantaloupe, honeydew melon, zucchini, and cucumbers) and bananas (105). PFAS has been described with ingestion of apples (106), carrots, parsnips, celery, hazelnuts, potatoes (107,108), celery (109), and kiwi (110) in patients sensitive to the major birch pollen, *Bet v 1*. Similarly, ingestion of apples, tree nuts, peaches, oranges, pears, cherries, fennel, tomatoes, and carrots has been associated with PFAS symptoms in patients allergic to tree and grass pollens (111). Typically, PFAS symptoms resolve rapidly without treatment and rarely involve any other target organs. However, certain associations, such as between celery tuber (celery root) and birch pollen, have been reported to cause severe systemic symptoms in some pollen-allergic patients (109). These more severe symptoms may be explained by the presence of both heat-labile and heat-stable proteins (112).

NON–IMMUNOGLOBIN E–MEDIATED FOOD ALLERGY

Food Protein–Induced Enterocolitis Syndrome

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated inflammatory disease of the entire gastrointestinal tract. FPIES typically occurs in infants by 4 to 6 months of age and is extremely rare in breastfed infants (113–115). The most common food triggers in FPIES are cow's milk and soy; consequently, the onset of symptoms often correlates with the introduction of infant formula in the first months of life. Although less common, solid foods can also be a trigger with rice being most commonly reported (116). Symptoms consist of profuse vomiting and diarrhea within 2 to 3 hours of eating the offending food protein, which can lead to profound dehydration and lethargy.

With chronic exposure, failure to thrive and hypoalbuminemia can be observed. Removal of the causal food results in the resolution of clinical symptoms. Being a non–IgE-mediated food allergy, skin tests and serum food–specific IgE tests are not helpful and would be expected to be negative. Instead, the diagnosis is made primarily through clinical history and symptoms with OFCs reserved for equivocal cases. Treatment of patients with FPIES consists of vigorous intravenous hydration and elimination of the offending food protein. Resolution of clinical reactivity typically occurs by 3 years of age.

Food Protein–Induced Proctocolitis

Food protein–induced proctocolitis, formally known as allergic proctocolitis, is another non–IgE-mediated inflammatory disease primarily affecting the distal colon. It usually presents within the first 8 weeks of life, with clinical symptoms involving blood streaked, loose stools with or without diarrhea in an otherwise healthy-appearing infant (117). In contrast to FPIES, food protein–induced proctocolitis occurs commonly in breastfed infants (i.e., up to 60%) as well as in cow's milk or soy milk formula–fed infants. Cow's milk has been found to be the most common food trigger (118). As with FPIES, the diagnosis is made by clinical history, and specific IgE measurements are typically negative. The differential diagnosis includes anal fissures, gastrointestinal infections, necrotizing enterocolitis, and intussusception. Treatment consists of elimination of the responsible protein, use of casein hydrolysate formulas, and in rare cases, use of amino acid–based formulas. Clinical symptoms typically resolve by 1 year of age.

Celiac Disease

Celiac disease is a non–IgE-mediated food allergy characterized by small intestinal mucosal injury and nutrient malabsorption in genetically susceptible individuals in response to the dietary ingestion of gluten-containing grains, especially wheat, rye, and barley (119,120). Immune responses to key gliadin epitopes are recognized as important in celiac disease pathogenesis. There is a strong human leukocyte antigen (HLA) association with HLA-DQ2 and HLA-DQ8 molecules, but human HLA-DQ risk factors do not explain the entire genetic susceptibility to gluten intolerance (121). Lesions of the small intestine are contiguous and most often involve the mucosa only, sparing the submucosa, muscularis, and serosa (122). A classic endoscopic finding in celiac disease is atrophy or flattening of the intestinal villi (123). The lamina propria is hypercellular, with a predominance of lymphocytes and plasma cells (122,123),

and there is a predominance of IgA-producing cells (124).

In addition to the classic intestinal lesions, serologic markers are often present in this disease. There are IgA antibodies found against reticulin and smooth muscle endomysium (125). IgA against the endomysium and tissue transglutaminase contained within the endomysium have been reported to be both sensitive and specific for the evaluation of celiac disease (126,127). On the other hand, anti-gliadin antibodies have been found to have poor positive predictive value (128).

Clinical symptoms of celiac disease are those of malabsorption, and the severity of symptoms correlates directly with the amount of intestine involved. Patients have profuse watery diarrhea, but extraintestinal manifestations, such as weight loss, poor growth, glossitis, and osteopenia reflecting severe malabsorption, may also be present (129). Interestingly, increasing numbers of individuals with atypical or asymptomatic celiac disease are being reported (120,130).

Dermatitis Herpetiformis

Dermatitis herpetiformis is a cutaneous manifestation of gluten sensitivity that is often associated with celiac disease. It is also occasionally associated with other autoimmune disorders and reportedly associated with an increased risk of lymphoproliferative disorders (131,132). It occurs most commonly in children 2 to 7 years of age. The rash is an erythematous, pleomorphic pruritic eruption involving predominantly the knees, elbows, shoulders, buttocks, and scalp; mucous membranes are spared. Lesions can be urticarial, papular, vesicular, or bullous (133). Although endoscopic findings of celiac disease are often present, most patients with dermatitis herpetiformis do not demonstrate clinical symptoms of celiac disease. Lesions respond to gluten elimination but often require considerable time to achieve full remission (134). As a result, sulfones, which typically relieve pruritic symptoms within 24 hours (133), are also an integral part of therapy for most patients.

DIAGNOSIS

The diagnostic approach to adverse food reactions begins with the medical history and physical examination and, if indicated, laboratory studies. The value of the medical history is largely dependent on the patient's recollection of symptoms and the examiner's ability to differentiate between disorders provoked by food hypersensitivity and other etiologies. Unfortunately, obtaining accurate

information is often difficult and several series demonstrated that less than 50% of reported food allergy could be verified by DBPCFC. The information required to establish that a food-allergic reaction occurred and to construct an appropriate blinded challenge to confirm the reaction if necessary, include the following: (a) the food presumed to have provoked the reaction, (b) the quantity of the suspected food ingested, (c) the length of time between ingestion and development of symptoms, (d) whether similar symptoms developed on other occasions when the food was eaten, (e) whether other factors (e.g., exercise) are necessary, and (f) how long since the last reaction to the food occurred. Although any food may cause an allergic reaction, a few foods account for about 90% of reactions: in adults—peanuts, nuts, fish, and shellfish; in young children —eggs, milk, peanuts, soy, and wheat (fish in Scandinavian countries). In chronic disorders (e.g., atopic dermatitis, asthma, chronic urticaria), history is often an unreliable indicator of the offending allergen.

Diet Diaries

Diet diaries are frequently discussed as an adjunct to history. As opposed to the medical history, it collects information on a prospective basis and is not as dependent on a patient's memory. Patients are instructed to keep a chronologic record of all foods ingested over a specified period of time. Unfortunately, only occasionally does this method detect an unrecognized association between a food and a patient's symptoms.

Elimination Diets

Elimination diets are frequently utilized both in the diagnosis and management of adverse food reactions. Once certain foods are suspected of provoking allergic disorders, they are completely omitted from the diet. The success of these diets depends on the identification of the correct allergen(s), the ability of the patient to maintain a diet completely free of all forms of the offending allergen, and the assumption that other factors do not provoke similar symptoms during the period of study. An elimination diet should be conducted for 1 to 2 weeks in suspected IgE-mediated disorders and for food-induced enterocolitis and colitis. Diets may need to be extended for up to 12 weeks in other gastrointestinal disorders, following appropriate biopsies. If no clear improvement is noted, it is less likely that food allergy is involved. However, in mixed immune food allergies, such as atopic dermatitis and chronic asthma, other precipitating factors may make it difficult to discriminate the effects of the food allergen from other provocative factors. In general, elimination diets alone are rarely diagnostic of food allergy.

Skin-Prick Testing

Skin-prick tests are reproducible (135) and frequently utilized to screen patients with suspected IgE-mediated food allergies. Glycerinated food extracts (1:10 or 1:20) are tested alongside appropriate positive (histamine) and negative (saline) controls. The criteria established by Bock and May (136) 40 years ago for interpreting skin-prick tests remains the standard with any food allergens eliciting a wheal at least 3 mm greater than the negative control being considered positive.

When interpreting skin-prick testing, it is important to keep in mind first, that a positive skin-prick test demonstrates the presence of allergen-specific IgE and second, that IgE is necessary but not sufficient for an IgE-mediated food-allergic reaction. As such, a positive skin-prick test should be interpreted as indicating the *possibility* that the patient has symptomatic reactivity to the specific food, whereas negative skin tests more confidently rule out the possibility of IgE-mediated reactions (negative predictive value > 95%), if good quality food extracts are utilized (136–140).

There are exceptions to this general statement: (a) the commercial extracts commonly used in testing can potentially lack the relevant allergen especially with less common allergens (141) or have the allergen but in a nonintact form owing to the lability of the responsible allergen (111); (b) children less than 2 years of age may have less skin reactivity, resulting in a negative or small wheal size despite a strong histories suggestive of IgE-mediated food allergy (142).

As a positive skin test only demonstrates the presence of allergen-specific IgE but not necessarily clinical allergy, investigators have been interested in determining predictive values based on mean wheal diameter. Recent studies have reported that for the diagnosis of cow's milk, hen's egg, and peanut allergy, skin-prick tests inducing mean wheal diameters >8 mm correlate with a >95% positive predictive value for clinical reactivity (143–145).

Intradermal skin testing is more sensitive than the skin-prick test when detecting specific IgE but is much less specific when compared to the DBPCFC (136). No patients with a positive intradermal skin test to a food and a concomitant negative skin-prick test have been shown to have a positive DBPCFC. In addition to its poor predictive value, intradermal skin testing can significantly increase the risk of inducing a systemic reaction compared to skin-prick testing and, therefore, is not recommended.

Atopy Patch Test

The atopy patch test (APT) is a means of testing for delayed-type hypersensitivity reactions and has been considered for the diagnosis of non–IgE-mediated food allergy (146–149). In a recent study of children with atopic dermatitis, the investigators concluded that the patch test added little diagnostic benefit compared to standard diagnostic tests (150). Several studies looking at APT for the identification of food triggers in eosinophilic esophagitis have suggested a potential role (151–153); however, further study is needed before it can be recommended for regular use.

In Vitro Allergen-Specific Immunoglobin E Tests

In vitro allergen-specific IgE tests (including radioallergosorbent test [RAST]; enzyme-linked immunosorbent assay; CAP System FEIA and UniCAP [Phadia; Uppsala, Sweden]; Magic Lite; ALK-Abello, Denmark) are utilized for measuring serum for IgE-mediated food allergies. Although generally considered slightly less sensitive than skin tests, one study comparing Phadebas RAST with DBPCFCs found skin-prick tests and RASTs to have similar sensitivity and specificity to food challenge outcome when a Phadebas score of 3 or greater was considered positive (137). In the past 10 years, the use of a quantitative measurement of food-specific IgE antibodies (CAP System FEIA or UniCAP) has been shown to be predictive of symptomatic IgE-mediated food allergy (154,155) (Table 18.5). Food-specific IgE levels exceeding the diagnostic values established as cutoff points indicate that the patient is greater than 95% likely to experience an allergic reaction if he or she ingests the specific food. In addition, the IgE levels can be monitored and if they fall to less than 2 kU_A/L for eggs, milk, or peanuts, the patient should be rechallenged to determine whether he or she has "outgrown" their food allergy (155–157).

The ability to measure IgE specific to individual allergens within certain foods has recently become commercially available and is referred to as component-resolved diagnostics (CRD). Studies have demonstrated predictive values for CRD in the diagnosis of certain food allergies, such as peanut and hen's egg allergy (158,159). However, CRD has not been shown to perform better than currently available food extracts to be recommended for regular use (160).

TABLE 18.5 FOOD-SPECIFIC IgE ANTIBODIES: DIAGNOSTIC UTILITY TO PREDICT A POSITIVE FOOD CHALLENGE

Cow's Milk	
IgE ≥ 15:	95% PPV
IgE ≥ 5:	95% PPV (age < 2 y)
Egg	
IgE ≥ 7:	95% PPV
IgE ≥ 2:	95% PPV (age < 2 y)
Peanut	
IgE ≥ 14:	95% PPV
Tree Nuts	
IgE ≥ 15:	95% PPV
Fish	
IgE ≥ 20:	95% PPV

IgE, immunoglobin E; PPV, positive predictive value.

Oral Food Challenge

The DBPCFC has been labeled the "gold standard" for the diagnosis of food allergies; it controls for the variability of chronic disorders like urticaria and other precipitating factors such as psychogenic (161). Many investigators have utilized DBPCFCs successfully in children and adults to examine a variety of

food-related complaints (162–165). However, the time required to perform both a suspect food and placebo challenge, difficulty in many cases of finding an appropriate placebo, and the need for a third party to maintain blinding make DBPCFCs impractical for everyday clinical use. As a result, open or occasionally single-blind food challenges are much more commonly used in clinical settings with DBPCFCs mostly reserved for research studies.

The selection of foods to be tested in DBPCFCs is based on patient history and usually skin test or *in vitro* specific IgE results. Prior to undertaking an OFC, several factors need to be taken into consideration. Suspect foods should be eliminated for 7 to 14 days prior to challenge, longer in some non–IgE-mediated gastrointestinal disorders. Antihistamines should be discontinued long enough to establish a normal histamine skin test, typically 2 to 3 days for first-generation H_1 antihistamines and 5 to 7 days for second-generation H_1 antihistamines. In some asthmatic patients, short bursts of corticosteroids may be necessary to insure adequate pulmonary reserve (forced expiratory volume in 1 second [FEV_1] > 70% predicted) prior to the OFC.

The food challenge is administered in the fasting state, starting with a dose unlikely to provoke symptoms (166). Many different dosing schedules have been suggested in the literature, but generally speaking, doses are gradually escalated and administered about every 15 minutes over a 90-minute period. A joint expert panel in 2012 consisting of American and European academic allergy societies sought to address the variation in protocols by releasing consensus guidelines referred to as PRACTALL (167). An OFC by PRACTALL guidelines includes the following doses: 3, 10, 30, 100, 300, 1,000, and 3,000 mg of food protein. Once the patient has tolerated all of the lyophilized food, clinical reactivity is generally ruled out. If a challenge is performed using a food in a form that is not typically eaten, a negative result should be confirmed by an open feeding of the food in a typically ingested form to rule out the possibility of a false-negative result because of alteration of the food allergen.

The length of observation after an OFC is typically dependent on the type of reaction suspected, for example, generally up to 2 hours for IgE-mediated reactions, up to 4 to 8 hours for milk-induced enterocolitis, and 3 to 4 days for allergic eosinophilic gastroenteritis. Results of blinded challenges for objective signs and symptoms are rarely equivocal, but can be made more objective by monitoring a variety of laboratory parameters, such as plasma histamine, pulmonary function tests, and nasal airway resistance; serum β-tryptase is rarely shown to rise following food-allergic reactions (71,168).

In non–IgE-mediated food allergies (e.g., dietary protein–induced enterocolitis), allergen challenges may require up to 0.15 to 0.3 g of food/kg of body weight given in one or two doses (169,170). In other non–IgE-mediated disorders (e.g., allergic eosinophilic esophagitis or gastroenteritis), the patient may require several feedings over a 1- to 3-day period to elicit symptoms. In most IgE-mediated disorders, challenges to more foods often may be conducted every 1 to 2 days, whereas with non–IgE-mediated disorders, challenges to new foods often need to be at least 3 to 5 days apart.

OFCs should be conducted in a clinic or hospital setting, especially if an IgE-mediated reaction or a dietary protein-induced enterocolitis is suspected, and only when trained personnel and equipment for treating systemic anaphylaxis are immediately available (162,171). Patients with histories of life-threatening anaphylaxis should be challenged only when the causative antigen cannot be conclusively determined by history and laboratory testing, or the patient is believed to have "outgrown" his or her sensitivity. The evaluation of many so-called delayed reactions (e.g., most IgE-negative gastrointestinal allergies) can be conducted safely in a physician's office, except perhaps for FPIES where intravenous access is generally required because of the risk of hypotension.

Practical Approach to Diagnosing Food Allergy

The diagnosis of food allergy remains a clinical exercise primarily dependent on a careful history. For IgE-mediated and mixed immune food allergy, selective skin tests and *in vitro* measurement of food-specific IgE can then be used to confirm the diagnosis by establishing the presence of food-specific IgE (156). When the history is less clear or in the case of non–IgE-mediated food allergy, a targeted exclusion diet can help to determine whether an association between the food and the patient's symptoms exists. Unfortunately, elimination diets are unable to prove causality and thus are not commonly diagnostic. Ultimately, an OFC, with its inherent risks, may be needed to make the diagnosis.

At the present time, there are no controlled trials supporting the diagnostic value for food-specific IgG or IgG_4 antibody levels, food antigen–antibody complexes, evidence of lymphocyte activation (^{3}H uptake, IL-2 production, leukocyte inhibitory factor production), or sublingual or intracutaneous provocation.

TREATMENT

Once the diagnosis of food allergy is established, the only proven therapy

continues to be strict *elimination* of the offending allergen. In the case of IgE-mediated food allergy, avoidance is coupled with ready access to self-injectable epinephrine for the treatment of allergic reactions. Patients and their families must be educated about how to avoid accidental ingestion of food allergens and to recognize early symptoms of an allergic reaction, in particular those that may herald the onset of an anaphylactic reaction. Patients must learn to read all food ingredient labels for the presence of specific food allergens, to become familiar with situations where cross-contamination is likely, and to avoid high-risk situations, such as buffets, ice cream parlors, and unlabeled candies and desserts (172). Numerous label reading patient resources have been created, and the Food Allergen Labeling and Consumer Protection Act passed in 2004 has helped in the identification of food allergen ingredients; however, accidental ingestions and reactions have continued to occur (173).

Patients with multiple food allergies, especially children, are at risk for nutritional deficiencies resulting from their restricted diets. If feasible, it is important to utilize the services of a nutritionist for education of the patient and family. Their help in managing the patient's diet is extremely important to ensure that there is adequate nutritional intake while on a restricted diet.

An emergency treatment plan indicating symptoms that require treatment with an oral antihistamine (preferably liquid diphenhydramine or cetirizine) or self-injectable epinephrine or both should be provided to the patient. Templates of anaphylaxis emergency treatment plans are readily available at patient advocacy and academic allergy society websites. The use of the epinephrine autoinjector should be demonstrated to the patient (and caregivers) and the technique reviewed periodically. At every physician encounter, patients should be reminded about the importance of having their emergency medications with them at all times and to check the expiration dates of their autoinjectors. Patients must also be instructed to seek evaluation at an emergency department or contact emergency services following the use of epinephrine, because there is an approximate 20% risk of recurrence of allergic symptoms following initial improvement with or without treatment (the so-called *biphasic anaphylaxis*).

Case reports on the use of immunotherapy for food allergy have sporadically been in the medical literature (174,175), but over the past 10 years, the interest in food immunotherapy has grown significantly. Traditional subcutaneous immunotherapy was attempted for peanut allergy, and despite some suggestion of clinical improvement, the significant numbers of adverse events associated with dosing has discouraged further research into this modality (176,177).

Attention has instead primarily focused on orally ingested food treatment termed oral immunotherapy (OIT). Several open and blinded studies in cow's milk, hen's egg, and peanut allergy have demonstrated the ability of OIT to induce desensitization defined as an increase in the threshold of food required to induce a clinical reaction while on active therapy (178–181). Concurrent immunologic changes in these studies have suggested a modulation of the immune response and the potential for a lasting response. To date, it has not been proven that OIT can induce true immunologic tolerance; however, the desensitization effect may last for a prolonged but finite amount of time after discontinuation of the therapy, an effect called sustained unresponsiveness (179,182). Unfortunately, these promising results have been tempered by concerns about the risks of therapy; most importantly, the potential development of eosinophilic esophagitis (183).

Alternative modalities of immunotherapy have more recently been investigated, including sublingual immunotherapy and epicutaneous immunotherapy. These modalities provide an easier method of administration and potentially an improved safety profile because of the lower doses typical of these therapies. Early studies have suggested the ability to induce desensitization, but the effect may be less robust than seen with OIT (184,185). Further research is needed to understand the magnitude and duration of the desensitization effect, the potential for tolerance, and, most importantly, the risk profile before any of these treatments can be recommended for clinical practice.

Another approach that has been investigated for food allergy is the use of anti-IgE antibody therapy. Studies on the use of anti-IgE therapy as monotherapy for the treatment of peanut allergy were inconclusive. However, results on the use of anti-IgE therapy in combination with OIT have suggested improved safety and short-term efficacy over OIT alone (186,187). Ultimately, the treatment for food allergy may involve combinations of available therapies potentially tailored to the individual patient.

PREVENTION

The role of dietary manipulation in the prevention of atopic disease in infants of allergic parents has been debated for many years (188). Delayed introduction of highly allergenic foods was recommended until recently as the safest approach that could also potentially prevent the development of allergy (189). Further consideration of these guidelines in 2008 concluded that there was insufficient evidence to support delayed introduction and led to the removal of these

recommendations from general pediatric feeding guidelines (188).

In direct contrast to these previous guidelines, an interesting epidemiologic study suggested that early, not delayed, introduction could provide a protective effect against the development of food allergy. Jewish children living in the United Kingdom and Israel were compared for their peanut introduction behaviors and subsequent rates of peanut allergy. Significantly higher rates of peanut allergy were found in the children living in the United Kingdom. Because the cohorts had similar genetic backgrounds, the primary difference between the groups was thought to be the routine introduction of peanut in early infancy in Israel compared to the delayed introduction common in the United Kingdom (190).

The Learning Early About Peanut allergy study was designed to prospectively investigate this finding and demonstrated a significantly lower rate of peanut allergy in high-risk children who introduced peanut in early infancy and maintained routine peanut dosing up to 5 years of age (191). This protective effect was shown to persist even after discontinuing peanut dosing for 1 year (192). Although the generalizability of these results has been questioned by some, these groundbreaking results leave little justification for the delayed introduction of peanut and, on the contrary, support the early introduction of peanut and potentially other highly allergenic foods.

NATURAL HISTORY

The vast majority of childhood food allergies are lost over time, although certain food allergies tend to persist, such as those to peanuts, tree nuts, fish, and shellfish (82,193–198). Of note, even after the development clinical tolerance, the presence of IgE, as detected by skin test or RAST, has been found to persist in IgE-mediated food allergy (199–201). For hen's egg allergy, the majority of cases resolve within a few years (202,203); however, patients with an egg-specific IgE level greater than 50 kU/L seem less likely to develop egg tolerance (204).

Cow's milk allergy affects 2.5% of children younger than 2 years of age (205,206). The potential for persistence of cow's milk allergy along with cow's milk–specific IgE levels effect on prognosis should be taken into consideration when counseling families regarding expected clinical outcomes (207). Non–IgE-mediated cow's milk allergy is typically a transient childhood condition that is almost always outgrown but must be managed carefully because challenges can be hazardous. IgE-mediated cow's milk allergy may persist in up to 20% of

children. It has been thought that in children with cow's milk or hen's egg IgE-mediated sensitivity, those who became tolerant had antibodies to conformational epitopes, whereas those with persistent hypersensitivity reacted primarily to linear epitopes (37).

Peanut and tree nut allergies affect about 0.5% to 1.3% of children and may be increasing over time (48,197,208). It is likely to be a lifelong disorder for most patients, although 20% to 25% outgrow peanut (197,209–211) and up to 9% outgrow tree nut allergies (193). A peanut-specific IgE of 2 kU/L has been shown to correlate with a 50% chance of passing an OFC (156,197), and thus IgE levels <2 kU/L would suggest a trend towards resolution of the allergy. Immunodominant IgE epitopes of the major peanut allergens *Ara h 1* (recognized by >90% of peanut-allergic individuals) and *Ara h 2* are linear (212,213) and may explain the persistence of peanut allergy. A food allergy rarely recurs once it has resolved; however, recurrence has been documented in unusual cases with peanut and tree nut (214).

SUMMARY

Food allergy is a common medical problem seen particularly early in life. Many of the common food allergies are outgrown in the first few years of life. Ingestion of foods in an allergic individual can quickly provoke cutaneous, respiratory, and gastrointestinal symptoms, and in a subset of patients, anaphylaxis can occur. Recent research has continued to characterize the various food hypersensitivity disorders, but our understanding of the basic immunopathologic mechanisms remains incomplete. Recent research has suggested that food allergy may possibly be prevented with dietary therapy. For those who go on to develop food allergy, the future seems bright because new forms of therapy continue to be studied and approved treatments seem to be on the horizon.

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SECTION V

Asthma

CHAPTER 19

Asthma

PAUL A. GREENBERGER AND WHITNEY W. STEVENS

■ OVERVIEW

Asthma is a disease characterized by hyperresponsiveness of bronchi to various stimuli, airways inflammation, and changes in airway resistance, lung volumes, and inspiratory and expiratory flow rates, resulting in symptoms of cough, wheezing, dyspnea, or shortness of breath. There are wide variations of resistance to airflow on expiration (and inspiration) with remarkable transient increases in certain lung volumes, such as residual volume (RV), functional residual capacity (FRC), and total lung capacity. In 1991, a National Institutes of Health (NIH) Expert Panel suggested that asthma was a disease characterized by (a) airway obstruction that is reversible—partially or completely, (b) airway inflammation, and (c) airway hyperresponsiveness (1). In 1997, the Expert Panel 2 Report described asthma as follows:

> Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with

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widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma (2).

The NIH Expert Panel 3 Report of 2007 confirmed this working definition (3). As of 2016, the Global Initiative for Asthma proposed the definition as follows:

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation (4).

Asthma, which can be considered intermittent or persistent, has been described or characterized by other designations, including allergic bronchitis, asthmatic bronchitis, allergic asthma, atopic asthma, nonallergic asthma, reactive airways disease, cough equivalent asthma (5–7), and cardiac asthma (8–10). A central feature of asthma from a physiologic viewpoint is bronchial hyperresponsiveness to stimuli, such as histamine or methacholine. In population screening, such nonspecific hyperresponsiveness has been reported as sensitive but not specific. However, caution is required in that in a study of 150 adolescents nearly 18 years of age who were transferred from pediatric to adult care, 29% of those patients with a diagnosis of asthma did not have bronchial hyperresponsiveness (11).

Asthma is considered, for most patients, a reversible obstructive airway disease as compared with chronic obstructive pulmonary disease (COPD). Many patients with asthma experience symptom-free periods of days, weeks, months, or years in between episodes, whereas chronic symptoms and fixed dyspnea characterize COPD. When daily symptoms of cough, wheezing, and dyspnea have been present for months in a patient with asthma, bronchodilator nonresponsiveness may be present. However, effective anti-inflammatory therapy, such as with a course of prednisone and/or inhaled corticosteroid (ICS)/long-acting β-adrenergic agonist with or without a leukotriene receptor antagonist or biosynthesis inhibitor or muscarinic antagonist, reduces symptoms and improves the quality of life along with improvement in pulmonary function status. Asthma–COPD overlap syndrome can be suspected when there is a history of asthma and cigarette smoking, and strong bronchodilator response to

albuterol (for forced expiratory volume in 1 second [FEV_1] $\geq$ 15% and $\geq$400 mL) with evidence of obstruction (FEV_1/forced vital capacity [FVC] < 0.70) (12).

Immunoglobulin E (IgE)-mediated bronchoconstriction can be demonstrated in many patients with asthma, but not all cases of asthma are "allergic." It is thought that about 80% of patients with persistent asthma have allergic asthma. In the Inner-City Asthma Study of children aged 5 to 11 years, 94% of children reacted to at least one allergen (13). Some evidence does exist for IgE antibodies to respiratory syncytial virus (RSV) (14) and parainfluenza virus (15); however, not all studies are consistent with this mechanistic explanation of antiviral IgE-mediated asthma. Alternatively, RSV infection supports T_H2 polarization of the immune response with reduced antiviral interferon-γ (IFNγ) production, and rhinovirus infection causes increased interleukin 33 (IL-33) production, the latter supporting T_H2 inflammation (16). There is reduced generation of antiviral IFNs when there is activation of the high-affinity receptor for IgE (Fcε RI) by allergen in plasmacytoid dendritic cells (17). In other words, allergen IgE activation of Fcε RI can decrease the innate immunity system's generation of antiviral IFNs. A clinical analogy of this observation is from a study where omalizumab was administered for 4 months to prevent seasonal exacerbations of asthma. Good responders to omalizumab were characterized by robust increases in *in vitro* IFNα from peripheral blood mononuclear cells during rhinovirus exposure (18). Furthermore, rhinovirus can increase activity of basophils (19).

The heritability (fraction of asthma that can be attributed to genetics aka genetic susceptibility) is 0.54 based on 71 studies of twins (20). Further, there is evidence that heritability of asthma is increasing over time (21,22). In monozygotic twins, there is a stronger correlation between the age of onset of asthma in the first twin with onset in the second (less waiting time) as compared with the sequence in dizygotic twins. There is a greater degree of concordance of severity of asthma in monozygotic compared to dizygotic twins (21).

The sudden onset of wheezing dyspnea that occurs within 3 hours of ingestion of aspirin or other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) (23) is not an IgE-mediated reaction but represents alterations of arachidonic acid metabolism, such as blockage of the cyclooxygenase pathway with shunting of arachidonic acid into the lipoxygenase pathway. Potent lipoxygenase pathway products, such as leukotriene D_4 (LTD_4), cause acute bronchoconstriction in aspirin- and NSAID–sensitive patients (23–26). Patients with aspirin-exacerbated respiratory disease have a "knock-in" condition in that there is

increased LTC_4 synthase in bronchial and nasal mucosa and elevated urinary concentrations of LTE_4, a metabolite of LTD_4, even at baseline (23,26). The concentrations of LTE_4 rise significantly after ingestion of aspirin or an NSAID in susceptible patients (23,25).

Many patients with asthma may have symptoms precipitated by nonspecific, non–IgE-mediated triggers, such as cold air, air pollutants including ozone (27), fine particles (<2.5 μm in diameter) (28), carbon monoxide (28), increased humidity (29), exercise, crying, or laughing. Psychologic stress such as from posttraumatic stress disorder (30,31), witnessing violence or other adverse domestic experiences (32) and sexual or physical abuse (33) are also associated with asthma. Lower concentrations of maternal umbilical cord 25-hydroxyvitamin D are associated with asthma (34).

GENETIC AND ENVIRONMENTAL FACTORS

Genetic and environmental factors are important individually in terms of development of asthma, but gene–environment interactions are operative (35). Heritability of asthma typically ranges from 30% to 87% (20). In a study of 4,910 4-year-old twins, heredity accounted for 68%, and the shared environment accounted for 13% (36). Nonshared environmental factors contributed 19% (36). The authors concluded that, "rearing environment, family diet, and air pollutants seem to play a minor role" (36). Having one or both parents with a history of asthma increases the risk of asthma in children (37). In some studies, the risk of a child having asthma is greater if there were maternal asthma compared with paternal asthma (38). But, similar risks have been noted (37). It is not always the case that having both parents with asthma increases the prevalence of childhood asthma. In twin studies, the concordance for asthma in monozygotic twins reared together has been found to be similar to that for twins reared apart (39). These data support a strong genetic effect on development of asthma. Both factors should be considered as contributory, and production of specific antiallergen IgE appears to be affected by environmental and local allergic exposures in the genetically susceptible subject.

Gene expression may be modified by the environmental influences including viral infections, termed epigenetics, where transcription is altered, resulting in differences in phenotypes (35). Table 19.1 presents some examples of loci and candidate genes for asthma (35). Single-nucleotide polymorphisms (SNPs) have been associated with asthma (35), and it is likely that more will be identified. However, the attributable risk from each SNP is small. When explored from the

perspective of gene–environment interactions, persuasive results have been identified in at-risk children (parent with allergies or asthma), who express specific genotypes *and* then experience human rhinovirus infections (40). With a variant SNP at locus 17q21 consisting of the TT homozygote at rs7216389, there was an odds ratio of 26.1 for developing asthma compared to 2.3 with the TT genotype alone or 5.2 for wheezing illnesses (40). Thus, in at-risk children, the human rhinovirus infection (but not RSV) can lead to childhood asthma (40).

The onset of early childhood asthma has been associated with smoking *in utero* (41), maternal, paternal, combined additive effects from maternal and paternal smoking, and a dose–response effect from parental smoking on asthma (42). For the development of severe asthma in children, cigarette smoking by grandparents has also been identified (43). However, once asthma begins, evidence exists for increased childhood respiratory symptoms from passive smoking and added deficits in lung function when there had been *in utero* smoking (44).

TABLE 19.1 EXAMPLES OF LOCI AND GENES ASSOCIATED WITH ASTHMA

LOCUS	GENE
17q12	GSDMB (Gastermin B)
2q12.1	IL1RL1 (IL-1 receptor–like 1)
22q12.3	IL2RB
6p21.3	HLA-DQB1
17q21.1	GSDMA (Gastermin A)
5q22.1	TSLP (thymic stromal lymphopoietin)
15q22.33	SMAD3 (SMAD family member 3)
7q22.3	CDHR3

9p24.1	IL-33
5q31.1	RAD50

Because the odds ratio of each locus is usually ≤1.2, the combined effects (if attempting to assign attributable risk) of several of these loci is small.

Adapted from Bonnelykke K, Ober C. Leveraging gene–environment interactions and endotypes for asthma gene discovery. *J Allergy Clin Immunol*. 2016;137:667–679.

Environmental factors, specifically viral infections, have been associated with the development of IgE antibodies. For historic perspective, in 1979, in a prospective study of high-risk infants, whose parents both had allergic diseases, Frick et al. (45) demonstrated development of serum antiallergen IgE contemporaneously in association with increasing antiviral (RSV, cytomegalovirus, and parainfluenza) antibodies. In 2010, it had been reported that the cytokine response to the viral infection can increase the number of available $Fc\varepsilon$ RI sites on monocytes and dendritic cells in the airway mucosa so that there will be increased antigen/allergen presentation (46). In addition, cells obtained from the sputum from children experiencing exacerbations of asthma have reduced generation of type I IFNs and T_H1 responses (47). Practically, croup in early childhood has been associated with subsequent development of asthma as have rhinovirus, RSV, coronavirus, influenza, parainfluenza virus, and metapneumovirus infections (48). These findings illustrate some of the interactions between family history, allergic sensitization, respiratory infections, and innate immune responses or lack thereof to viral infection on development of asthma.

Indoor allergen exposures from house dust mites, cats (some studies), rodents, molds, and cockroaches have been associated with the development of childhood asthma (49,50).

Children who have received whole organism vaccinations with measles, mumps, rubella, tick-borne encephalitis, and Bacille Calmette–Guérin (BCG) were at less risk of developing asthma compared to children who had not received these vaccinations (49).

Environmental or remediable influences can not only be predisposed to development of asthma but can also be associated with a reduced risk of asthma (49). In particular, in a birth cohort study up to 20 years of age in Germany, the

factors associated for asthma included having parents with asthma, allergic rhinitis or eczema, starting day care *between* 1.5 and 3.0 years of age, having a mother who smoked during the pregnancy (25 cigarettes/day or more), and having been born into a family in the lower economic range (for either parents' or grandparents' net income) (49). There was reduced risk of asthma when children had been vaccinated with live vaccines as mentioned, had not been exposed to tobacco when *in utero,* and in which they began day care either earlier than 1.5 years or greater than 3.0 years of age (49). In this study, the following variables were not associated with increased risk of asthma: pets at home, the presence of older siblings, being breastfed, and passive smoking (49).

The notion of the "hygiene hypothesis" is that there are beneficial effects of microbes in the home that do not cause any recognizable infection or illness (51). The "protective" home environments (containing high concentrations of lipopolysaccharides) consist of stables and dairy farms that are part of the family home, which is built in an L shape. The home and barn are attached. The absence of such exposures would permit asthma or atopy. Some specific protective factors have been identified and include small-scale pig farming (<10 pigs/farm) but not sheep farming, raw milk consumption, and a child's involvement in frequent haying and staying in animal sheds (52). There remains some controversy about the "hygiene hypothesis" and development of asthma or atopy, but the microbe-rich environments seem to be protective against development of asthma by altering the predominant cytokines generated by $CD4^+$ lymphocytes and interactions with innate immunity and its Toll-like receptors (TLRs) (52). A process that favors asthma includes generation of the helper T-cell subset T_H2, which is central to IgE production, as opposed to T_H1, which would diminish an "atopic" pattern and contribute to a classic delayed-type hypersensitivity response (type IVa_1). In a study of 867 children in Japan who had received BCG immunization after birth and at 6 and 12 years of age, the presence of and induration of tuberculosis skin tests were studied in relation to the emergence of atopy (asthma, rhinitis, and atopic dermatitis) (53). By age 12 years, 58% of the children had developed positive (≥ 10 mm in duration) responses to tuberculin testing, and 36% of children had reported atopic symptoms (53). Asthma symptoms and atopy were associated negatively with positive tuberculin responses, and the presence of tuberculin reactivity was associated with remission from asthma by years 6 or 12 (53). The data raised the possibility that the T_H1 response produced by BCG immunization resulted in increases in the T_H1 cytokines, IFNγ, and IL-12 and decreases in incidence of asthma, possibly even inducing remissions of atopy. In addition, there were

reduced quantities of the T_H2 cytokines IL-4, IL-13, and IL-10, compared with the BCG nonresponders, who had more atopy and asthma. Alternatively, these data might be interpreted that children likely to become atopic have a reduced ability to develop T_H1 memory lymphocytes after BCG immunization or, by analogy, reduced response to measles vaccination (54). The latter stems from data revealing less atopy when there was a previous episode of measles (54). These studies and the association between RSV and rhinovirus infections and childhood asthma suggest that the critical link may be the predominance of the T_H1 cytokines and protective innate immune responses. The latter may be specific, such as for TLR 5 for people exposed to pigs and TLRs 6 and 8 for people working with silage (52).

In a comparison of two US agricultural populations, but in whom the farming practices contrasted, the prevalence of asthma (and associated allergic sensitization) was four to six fold less in Amish (northern Indiana) as compared to Hutterite (South Dakota) children (55). The Amish use horses for fieldwork and transportation, whereas the Hutterites live on large, industrialized farms. Endotoxin from house dust was 6.8 times greater in Amish homes (55). Monocytes from Amish children expressed lower numbers of human leukocyte antigen–antigen D-related molecules and the immunoglobulin-like transcript (ILT)3 (55). Similarly, there were fewer peripheral blood eosinophils and greater numbers of neutrophils in Amish children. One of the upregulated genes was TNFAIP3, which limits the activity of inflammatory pathways, leading to nuclear factor kappa B (NF-κB) (55). The data are consistent with the protective microbial environment in Amish ("hygiene hypothesis") or, by reverse causation, susceptibility to asthma might be attributable to children who have weak innate immune responses to microbes present in the environment.

The effects of indoor and outdoor air pollution on the early development of or aggravation of established asthma are very important (50,56). The effects of air pollution from ozone and small particles have been associated with hospitalizations for acute severe asthma (57).

COMPLEXITY OF ASTHMA

The cause of asthma remains unknown, although asthma is considered a very complex, heterogeneous, inflammatory disease. Some important pathologic findings include a patchy loss of bronchial epithelium, usually associated with eosinophil infiltration (58–61), neutrophilic infiltration (61), lymphocyte infiltration (58,59), mast cell degranulation (58–60), contraction and hypertrophy

of bronchial smooth muscles, bronchial mucosa edema and increased blood flow (62), bronchial gland hyperplasia, hypersecretion of thick bronchial mucus, and basement membrane thickening (58,59,63). Collagen synthesis may result from stimulation or injury to airway epithelial cells (64). One key cell is the myofibroblast, which is a hybrid cell of fibroblast and smooth muscle cell origins. These cells produce types III and I collagen (64). Epithelial cells obtained during bronchoalveolar lavage (BAL) from patients with asthma have been found to be much less viable than in subjects without asthma (65). However, the epithelial cells from patients with asthma produced much more (a) fibronectin, a glycoprotein involved with cell attachment, cell growth, and chemotaxis; and (b) 15-hydroxyeicosatetraenoic acid, a metabolite of arachidonic acid (65). The increased metabolic activity of epithelial cells appears to contribute to airway damage and remodeling. There is subepithelial "fibrosis" that is composed of collagen types I, II, and V, which contributes to the basement membrane thickening of asthma.

When bronchial biopsy samples were obtained from 14 patients who had asthma for 1 year or less, increases in numbers of mast cells, eosinophils, lymphocytes, and macrophages were found in the epithelium (66). Deeper in the lamina propria, eosinophils, lymphocytes, macrophages, and plasma cells were present, suggesting that patients with mild asthma, who had not received anti-inflammatory therapy, had marked cellular infiltration in the bronchial mucosa (66). It is known that treatment with ICS reduces the numbers of eosinophils and mast cells in the mucosa.

Human bronchial epithelium from patients with asthma expresses Fas ligand (Fas L) and Fas on eosinophils and T lymphocytes (67). Activation of Fas by Fas L induces apoptosis. Biopsy samples from patients, who had not received ICS, had reduced numbers of apoptotic eosinophils and reduced expression of Fas L and *Bcl-2*, which help regulate apoptosis. Conversely, ICS–treated patients had fewer eosinophils and increased numbers of apoptotic eosinophils (67). In a study of BAL of 12 newly diagnosed and untreated patients with asthma, reduced expression of messenger RNA (mRNA) for both Fas and the Fas receptor (CD95) on $CD3^+$ T lymphocytes was found (68). These findings are consistent with a persisting inflammatory cell infiltrate that characterizes asthma and offers the possibility of targeted anti-inflammatory therapy.

Some physiologic characteristics of asthma include bronchial hyperresponsiveness to stimuli such as histamine (69), methacholine (70), or LTD_4 (71) and at least a 12% improvement in FEV_1 after inhalation of a β_2-

adrenergic agonist, unless the patient is experiencing acute severe asthma (status asthmaticus) or has had severe, ineffectively treated airway obstruction. There are large changes in lung compliance, depending on the severity of the disease.

On a cellular level, during acute episodes of asthma, there are activated or hypodense eosinophils present in increased numbers (72–74) and hyperadhesive eosinophils in the sense of increased binding to vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (74). Eosinophil products such as major basic protein (MBP) can be identified in sputum (73) and is present in areas where bronchial epithelium has been denuded. Eosinophil cationic protein (ECP) has also been identified in areas of denuded bronchial epithelium. ECP has been reported to be even more cytotoxic than MBP. Mast cells in the bronchial lumen and submucosa are activated, and their many cell products are released, whether preformed or synthesized *de novo*. Mast cells are found to be in close proximity to smooth muscle. Indeed, it has been suggested that the mast cells infiltrate smooth muscle causing "mast cell myositis" (75,76). Macrophages, lymphocytes, and epithelial cells participate as well, and when epithelial cells are damaged, the production of the protective PGE_2 is reduced. The epithelium is active immunologically because it can produce "upstream" effector molecules and cytokines, including IL 25, IL-33, and thymic stromal lymphopoietin (TSLP) that support or initiate T_H2 polarization (77). Supporting the biologic contribution of TSLP, when an anti-TSLP antibody was administered to research subjects, the early and late bronchial responses to inhaled allergen were reduced (77).

Evidence supports neuroimmunologic abnormalities in asthma, such as the lack of the bronchodilating nonadrenergic noncholinergic (NANC) vasoactive intestinal peptide (VIP) in lung sections from patients with asthma and reduced concentrations of VIP during acute exacerbations of asthma (78,79). There are increased concentrations of IgG autoantibodies that catalyze the hydrolysis of VIP in women whose asthma became more difficult to control during pregnancy (78). Substance P concentrations in induced sputum have been reported to be markedly elevated, compared with those in controls (80). The concentrations of the tachykinin, neurokinin A, is elevated in BAL fluid from patients with asthma compared to normal (81), and the potent vasodilator, calcitonin gene–related peptide, has been detected during late asthmatic reactions (82).

The free radical nitric oxide is detectable in expired air in patients with asthma, increases during exacerbations, and its concentration increases further after allergen challenge. It is a marker of T_H2 or type 2 persistent asthma. ICS,

such as fluticasone, result in about a 60% reduction in exhaled nitric oxide (eNO) within 6 weeks. It has been hypothesized that management of asthma could be improved by using the biomarker, eNO. Nevertheless, when asthma management compared the use of the National Asthma Education and Prevention Program Expert Panel (NAEPP) guidelines combined with measurement of eNO to the guidelines alone, there was no meaningful difference in control of asthma (83). A free radical generated from arachidonic acid, 8-isoprostane, is increased in asthma and reflects ongoing oxidative stress (84,85). There are progressively greater amounts in expired air as asthma severity increases from mild-to-severe or during exacerbations (84,85).

In addition to the abovemetioned features of asthma, asthma is heterogeneous in its clinical presentations (phenotypes) and responses to pharmacologic treatment. Patients vary in their responses to β_2-adrenergic agonists (86), ICS (87), leukotriene antagonists (88), oral corticosteroids (89), theophylline (90), and long-acting muscarinic antagonists (LAMAs) (91).

These findings demonstrate some but not all of the complexities of asthma, which decades ago was considered a psychologic condition. Asthma is not a psychologic disorder. Nevertheless, the burden of asthma as a chronic disease, especially when the patient has experienced hospitalizations or emergency department visits, has uncertainties about or lack of confidence about the security of personal control, or is a witness to or victim of violence, may result in psychologic disturbances or abnormal coping styles that coexist with asthma (92–94).

PREVALENCE AND SIGNIFICANCE

The prevalence of current asthma in the United States is 24 million people or 7.7% of the population as of 2014 consisting of 6.3 million children and 17.7 million adults (95). Considered by age groups, current asthma is present in 4.3% of children aged 0 to 4 years, 10.3% for 5 to 14 years, and 9.1% for 15 to 19 years (95). The current asthma prevalence in boys aged <18 years is 10.1% compared to 9.0% in girls. But the trend reverses because current asthma is present in 5.1% of men (ages $\geq$ 18 years) compared to 9.6% in similarly aged women (95). Asthma is much more prevalent in Puerto Rican Hispanics (ages < 18 years, 23.5%; age > 18 years, 13.3%) compared to Mexican Americans (ages < 18 years, 7.1%; age > 18 years, 4.9%) and Black non-Hispanic (ages < 18 years, 13.4%, age > 18 years, 8.7%) and White non-Hispanic (ages < 18 years, 7.6%; age > 18 years, 7.6%) (95). By socioeconomic status, the prevalence of

current asthma is 10.4% if the family is below 100% of the federal poverty level compared with 6.3% if family income is at least 450% of the same level.

There is a disportionate rate of hospital discharges for asthma (based on 2010 data) in that for Whites, the rate was 8.7 of 10,000 persons compared with 29.9 of 10,000 in Blacks (95). The rate for hospitalizations for asthma based on the population had remained unchanged during the period from 1980 to 2004 (96) despite vast increments in the knowledge of asthma. These data have been expressed differently in the past 10 years, but the data remain the same on a per population basis.

Fatalities from asthma in the United States in 2014 were 3,651 (187 in children and 3,464 in adults (age > 18 years) (95). The rate of fatalities from asthma increased in the United States from 0.8 deaths per 100,000 general population in 1977 to 2.0 in 1989, still 2.0 in 1997 (97). By 2014, the rate had declined to 1.1 per 100,000 population. By race, it was 0.9 per 100,000 for White non-Hispanic, 2.54 per 100,000 for Black non-Hispanic, and 0.8 per 100,000 for Hispanic (95).

The World Allergy Organization (WAO) has estimated that 300 million people worldwide have asthma, of which half are in developing countries, and that there are 250,000 premature deaths from asthma (98). By the year 2015, the WAO anticipates that 400 million people would have asthma. Many patients with asthma live in resource-poor countries and have governments who supply albuterol but not controller medications, such as ICS. There is a wide distribution of self-reported symptoms from asthma, such as quite low in Russia, Georgia, and Indonesia to high in the United Kingdom, Australia, and New Zealand (98).

Intermittent respiratory symptoms may exist for years before the actual diagnosis of asthma is made in patients, especially those older than 40 years of age. The diagnosis of asthma may be more likely made in women and nonsmokers, whereas men may be labeled as having chronic bronchitis, when in fact they do not have chronic sputum production for 3 months each year for 2 consecutive years. Asthma may have its onset in the geriatric population, and medication nonadherence and polypharmacy are found frequently (99). Asthma may begin during or after an upper respiratory tract infection, and the diagnosis can be delayed or overlooked. Treatment may be more complicated because of comorbidities and impaired cognition ("geriatric overload").

Asthma morbidity can be enormous from a personal and family perspective as well as from the societal aspect. The number of days of school missed from asthma is excessive, as is work absenteeism or presenteeism (present but not

fully productive). When children are ill from asthma, the parent may miss work, and the child doesn't attend school. In the United States, attacks of asthma are frequent because 48.0% of children/adolescents <18 years of age reported an episode in the previous year. Similarly, 43.6% of adults noted an acute attack (95).

Asthma may be work related. As of 2013, it was estimated that 5% to 10% of working adults in the United States had asthma that is caused or aggravated by an occupational exposure (100). Terminology includes "new-onset asthma" which consists of occupational asthma (*de novo* asthma related to exposures at work) or work-exacerbated asthma (preexisting or current asthma worsened by triggers related to employment (100). Workers in health care jobs are at increased risk of new-onset asthma because of exposures to cleaning and disinfection products, aerosolized medications, and allergens (100).

A disturbing finding was reported in a study of patients with asthma conducted in the Detroit area. Black patients received or filled fewer prescriptions for ICS and were less likely to be referred to an asthma specialist than Caucasians in the managed care setting in which the study took place (101). All the patients in this study were enrolled in the same large health maintenance organization; thus, factors such as insurance type or access to medications would not explain the discrepancy in care for Black patients as compared to Caucasians.

The costs of asthma include direct costs of medications, emergency department treatment, hospitalizations, physician or health professional charges, and laboratory testing in addition to indirect costs for time lost from work (absenteeism) and loss of worker productivity (presenteeism). It has been estimated that having asthma is associated with an additional $3,259 cost/year (102). The total cost of asthma in the United States in 2009 was $56 billion (direct costs and cost of lost productivity) based on 13.2 million people with asthma (102). Current total costs would be approximately double this number because the prevalence of asthma is almost 25 million in the United States. In a managed care setting, the cost/patient with severe uncontrolled asthma was $2,325 versus $1,056 for other patients with asthma (103). Some patients have been labeled as the "$100,000 asthmatic patients" because of repeated hospitalization and emergency department visits (104). Emotional costs of asthma are great for the sufferer and the family if asthma is managed ineffectively or if the patient refuses to adhere to appropriate medical advice.

The death of a family member or friend from asthma is shocking; the person

may be young, and the fatal attack may not have been anticipated by others or even the patient. It must be kept in mind that with current understanding and treatment of asthma, nearly all fatalities should be avoidable, and asthma need not be a fatal disease. More than half of the deaths from asthma occur outside the hospital. This observation has led some physicians to conclude that emergency medical services should be improved or even that every patient with asthma should receive a prescription for an albuterol metered-dose inhaler (MDI) or self-administered epinephrine. One cannot dispute such an argument about emergency services, but it is advisable for the physician or health care professional managing the patient with asthma to have an emergency plan (action plan) available for the patient or family so that asthma is not managed from a crisis orientation but rather on a preventive basis. Further, an education program or patient instructions can identify what patients should do when their medications are not effective, such as with a change in the level of control or for an exacerbation of asthma. In resource-poor countries, ICS may not be available. In resource-rich countries, the costs of medications may be prohibitive for patients.

ANATOMY AND PHYSIOLOGY

The central function of the lungs is gas exchange with delivery into the blood stream of oxygen and removal of carbon dioxide. The lung is an immunologic organ and has endocrine and drug-metabolizing properties that affect respiration. The lung consists of an alveolar network with capillaries passing near and through alveolar walls and progressively larger intrapulmonary airways, including membranous bronchioles (1 mm or smaller noncartilaginous airways) and larger cartilaginous bronchi and upper airways. Inspired air must reach the gas exchange network of alveoli. The first 16 airway divisions of the lung are considered the conducting zone, whereas subsequent divisions from 17 to 23 are considered transitional and respiratory zones. The conducting zone consists of trachea, bronchi, bronchioles, and terminal bronchioles and produces what is measured as airway resistance. The terminal bronchioles as a rule have diameters as small as 0.5 mm. Respiratory bronchioles, alveolar ducts, and sacs comprise the transitional and respiratory zones and are the sites of gas exchange (105).

The structures of bronchi and trachea are similar, with cartilaginous rings surrounding the bronchi completely until the bronchi enter the lungs, at which point there are cartilage plates that surround the bronchi. When bronchioles are about 1 mm in diameter, the cartilage plates are not present. Smooth muscle surrounds bronchi and is present until the end of the respiratory bronchioles.

The lining mucous membrane of the trachea and bronchi is composed of pseudostratified ciliated columnar epithelium. Goblet cells are mucin-secreting epithelial cells and are present in airways until their disappearance at the level of terminal bronchioles. In the terminal bronchioles, the epithelium becomes that of cuboidal cells with some cilia, Clara (secretory) cells, and goblet cells until the level of respiratory bronchioles, where the epithelium becomes alveolar in type. Mucus consists of a superficial gel phase composed of glycoproteins and a sol phase consisting of isotonic fluid in contact with the mucous membrane cells. The cilia move in the sol phase proximally to help remove luminal material (debris, cells, and mucus) by the ciliary "mucus escalator." Other cells such as mast cells, alveolar macrophages, polymorphonuclear leukocyte lymphocytes, eosinophils, and airway smooth muscle cells contribute to lung pathology in different ways. Epithelial cells may be thought of in a constant state of "injury" and are not able to be "repaired" completely. There is loss of columnar epithelial cells and the tight junctions. Permeability is increased. Primary bronchial epithelial cells from subjects with asthma have been shown to replicate rhinovirus *in vitro* to several logs, whereas those of normal control subjects were resistant to infection. This resistance was a result of rapid induction of apoptosis and of IFNβ in the normal cells, whereas these responses were deficient in asthmatic cells. These studies were extended to a family of three related proteins, the IFNγs 1 to 3, production of which was also deficient *in vitro* and related to asthma exacerbation severity *in vivo* (106,107). Rhinovirus induces a host response, including epithelium-derived IL-25, IL-33, and TSLP, that stimulate T cells and ILC-2 cells toward production of IL-4, IL-5, and IL-13, compatible with the T_H2 (type 2) response (107).

The bronchial wall is characterized by mucosa, lamina propria, smooth muscle, submucosa, submucosal glands, and cartilaginous plates. Submucosal glands produce either mucous or serous material depending on their functional type. Mast cells can be identified in the bronchial lumen or between the basement membrane and epithelium. They are "microlocalized" to smooth muscle cells and mucosal glands (108). Mast cells have been recovered from BAL samples but are low in number in these samples. Mast cell heterogeneity has been recognized based on contents and functional properties. Briefly, mucosal mast cells are not recognized in a formalin-fixed specimen, but connective tissue mast cells are. Mucosal mast cells are present in the lung and contain tryptase but not chymase, whereas connective tissue mast cells contain tryptase and chymase (109). Mast cells participate in airway remodeling because they activate fibroblasts (109,110) and infiltrate and interact with smooth muscle

cells (109,110), causing a "mast cell myositis" of the smooth muscle. Mast cell–derived tryptase is a mitogen for epithelial cells and stimulates synthesis of collagen (109). The mucosal mast cells are stimulated by IL-3, IL-4, and IL-9 (a growth factor for mast cells) (109). The submucosal (connective tissue) mast cells are present in large and small airways and are thought to participate in localized fibrogenesis (109). These mast cells interact with stem cell factor (c-kit ligand) and smooth muscle cells (109). In addition to mast cell generation of histamine, prostaglandin D_2 (PGD_2), LTD_4, and tryptase, they secrete IL-4, which upregulates VCAM on vessel endothelial surfaces. Eosinophil entry into tissues is facilitated by VCAM. IL-4 also favors isotype switching within the nucleus to cause production of IgE antibodies. The mast cell has many effects, from mediator release and cytokine production to fibrogenic activity. Their interactions with smooth muscle cells are intriguing in the context of induced "myositis" of the smooth muscle (109).

Neutrophils have been recovered in induced sputum using 3.5% saline in an ultrasonic nebulizer from patients with asthma (111,112). The numbers were increased in patients with severe asthma (53%) compared with moderate (49%) and mild (35%) asthma. Sputum from nonatopic, nonasthmatic subjects had 28% neutrophils (111). The concentrations of IL-8, which is chemoattractant for neutrophils and is an angiogenic cytokine, and of myeloperoxidase were increased in sputum from patients with moderate and severe asthma (111). Neutrophils have been identified in some (113) but not all (114) patients with sudden (<3 hours) death from asthma.

Macrophages serve as antimicrobial and pro-inflammatory cells and are accessory cells for presenting antigens. Macrophages are present in patients with asthma but are found in greater numbers in patients with chronic bronchitis. Macrophages have been detected during both early and late bronchial responses to allergens. These cells are metabolically active in that they can generate prostaglandins, leukotrienes, pro-inflammatory cytokines, chemokines, free radicals, and mucus secretagogues.

Increased numbers of eosinophils in bronchial biopsy specimens and sputum can be expected in many patients with asthma. It has been estimated that for every 1 eosinophil in peripheral blood, there are 100 to 1,000 in the tissue. Patients with mild asthma have eosinophils detected in bronchial biopsy samples, and eosinophils can be found in postmortem histologic sections (113,114). Eosinophils produce MBP, ECP, eosinophil-derived neurotoxin, eosinophil peroxidase, free radicals, leukotrienes, and T_H2 cytokines.

Eosinophils are pro-inflammatory cells that participate in the pathogenesis of airway remodeling in patients with persistent asthma.

Epithelial cells are shed especially in patients with severe asthma but even in patients with mild asthma. Besides being a physical barrier, the respiratory epithelium forms a tight junction and has antimicrobial and regulatory properties. There are a vast number of functions and interactions of epithelial cells (115–117). For example, one of many actions is to produce neutral endopeptidase, which degrades substance P. The loss of functioning epithelium could lead to potentiated effects of this neuropeptide. Similarly, epithelial cells generate smooth muscle–relaxing factors that could be decreased in amount as epithelium is denuded. Epithelial cell fluid obtained during BAL was analyzed for a gelatinase, which is in the family of matrix metalloproteinases (MMPs) (118). Mechanically ventilated patients with asthma were found to have very high quantities of a 92-kDa gelatinase, compared with patients with mild asthma and with ventilated, nonasthmatic subjects (118). This enzyme may damage collagen and elastin and the subepithelial basal lamina region (118). Increased permeability could result because of epithelial cell shedding and alterations of types IV and V collagens that are present in this basement membrane region (118). In this study, mechanically ventilated patients had increased numbers of eosinophils and neutrophils, compared with nonventilated patients with mild asthma (118). There was no difference in numbers of epithelial cells in BAL between patients with mild asthma and the mechanically ventilated patients with asthma, but both groups had twice the percentage as the nonasthmatic subjects, emphasizing that epithelial cell denudation occurs in mild as well as severe asthma. MMP-9, which is a gelatinase and type IV collagenase, is increased in expired breath condensates in association with the severity of asthma and compared to nonatopic controls (119). However, its inhibitor, tissue inhibitor of metalloproteinases (TIMP-1) did not differ according to the severity of asthma or in controls (119). Thus, in asthma, there is evidence for unneutralized MMP that facilitates destruction of collagen and elastin as part of the remodeling processes.

Whereas phenotypes of asthma can include the eosinophilic predominant, neutrophilic predominant, mixed eosinophilic/neutrophilic, and paucigranulocytic patterns, much remains to be clarified (120).

Innervation

The nervous system and various muscle groups participate in respiration. Efferent parasympathetic (vagal) nerves innervate smooth muscle cells and

bronchial glands. The vagus nerve also provides for afferent innervation of three types of sensory responses. The irritant (cough) reflex is rapidly adapting and originates in the trachea and main bronchi. Pulmonary stretch or slowly adapting afferents are also located in the trachea and main bronchi, whereas C fibers are located in small airways and alveolar walls. Afferent stimulation occurs through the carotid body (sensing oxygen tension) and nervous system chemoreceptors in the medulla (sensing hypercapnia).

Efferent respiratory responses include cervical and thoracic nervous system innervation of respiratory muscles. Fortunately, not all respiratory muscles are essential for respiration should a spinal cord injury occur. In addition to efferent parasympathetic innervation of smooth muscle cells and bronchial glands, another source of efferent stimulation is through the NANC epithelial sensory nerves. Stimulation of these nerves by epithelial cell destruction that occurs in asthma can trigger release of bronchospastic agonists, such as substance P and neurokinins (A and B), through an antidromic axon reflex. The bronchodilating NANC neurotransmitter, VIP, may oppose effects of other bronchoconstricting agonists, such as substance P. Nitric oxide is a mediator of the NANC system and could offset some of the bronchoconstriction induced by histamine and bradykinin (121). The absence of VIP could contribute to bronchoconstriction.

Smooth muscle cells participate in the Hering–Breuer inflation reflex, in which inspiration leading to inflation of the lung causes bronchodilation. This reflex has been described in animals and humans. The clinical significance in human respiratory disease may be minimal. For example, when a patient with asthma experiences bronchoconstriction when inhaling methacholine or histamine, there is increased airway resistance during a deep inspiration (122). In contrast, patients without asthma and those with rhinitis demonstrate bronchodilation and reduced airway resistance at total lung capacity. During a bronchial challenge procedure in a patient with rhinitis, if the patient performs an FVC maneuver by inhaling to total lung capacity after inhaling the bronchoconstricting agonist in question, the resultant *bronchodilation* may mask any current airway obstruction. To obviate this possibility, the initial forced expiratory maneuver should be a partial flow-volume effort, not a maximal one, which requires maximal inspiration. Otherwise, the dose of agonist necessary to achieve finally a 20% decline in FEV_1 will be higher than necessary.

PATHOPHYSIOLOGIC CHANGES IN ASTHMA

From a pathophysiologic perspective, the changes that occur in asthma are

multiple, diverse, and complex. Further, some of the abnormalities, such as bronchial hyperresponsiveness and mucus obstruction of bronchi, can be present when patients do not have symptoms. Major pathophysiologic abnormalities in asthma are (a) widespread smooth muscle contraction, (b) mucus hypersecretion, (c) mucosal and submucosal edema, (d) bronchial hyperresponsiveness, and (e) inflammation and remodeling of the airways. The concept of "airway remodeling" includes inflammation, mucus hypersecretion, subepithelial fibrosis, airway smooth muscle hypertrophy, and angiogenesis (3,4). Obstruction to airflow during expiration and inspiration results in greater limitation during expiration. Hypertrophy and even hyperplasia of smooth muscle have been recognized in asthma. Smooth muscle contraction occurs in large and/or small bronchi.

Bronchial challenge of patients with asthma by inhalation of histamine demonstrated two abnormal responses compared with patients without asthma. First, the patients with asthma have increased *sensitivity* to histamine (or methacholine) because a smaller-than-normal dose of agonist is usually necessary to produce a 20% decline in FEV_1. Second, the *maximal* response to the agonist in asthma is increased over that which occurs in nonasthmatic, nonrhinitic subjects. In fact, the maximal bronchoconstrictive response (reduction of FEV_1) that occurs in the nonasthmatic, nonrhinitis subject, if one occurs at all, reaches a plateau beyond which increases in agonist produce no further bronchoconstriction. In contrast, were it possible (and safe) to give a patient with asthma increasing amounts of an agonist such as histamine, or methacholine, increasing bronchoconstriction would occur. In an analysis of 146 patients with mild asthma who had undergone bronchial provocation challenge with histamine, two patterns were identified (123). The first was the decline of FEV_1 and FEV_1/FVC without a change in FVC at the dose of histamine, causing a 20% decline in FEV_1 (PC_{20}). The second pattern, detected at the time of the PC_{20} response, had reductions in FVC and FEV_1 but not FEV_1/FVC. It was concluded that the latter subjects experienced excessive bronchoconstriction (123). The authors identified a clinical connection in that there was a moderate correlation between the percentage decline in FVC at the PC_{20} and patients necessitating prescriptions for oral corticosteroids (but not β_2-adrenergic agonists) (123). In the patients who develop a declining FVC and FEV_1 after bronchoprovocation challenge, there is a concurrent increase in RV, which is detrimental if it continues. In summary from these findings, the ease of bronchoconstriction (PC_{20}) is one parameter, but the extent of

bronchoconstriction (drop in FVC), when the patient has reached the PC_{20}, correlated with need for oral corticosteroids.

Hypersecretion of bronchial mucus may be limited or extensive in patients with asthma. Autopsy studies of patients who died from asthma after having symptoms for days or weeks classically reveal extensive mucus plugging of airways. Large and small airways are filled with viscid mucus that is so thick that the plugs must be cut for examination (124). Reid (124) has described this pattern as consistent with endobronchial mucus suffocation. Other patients have mild amounts of mucus, suggesting that perhaps the fatal asthma episode occurred suddenly (over hours) and that severe bronchial obstruction from smooth muscle contraction contributed to the patient's death. A virtual absence of mucus plugging, called *empty airways* or *sudden asphyxic asthma*, has been reported (125). Desquamation of bronchial epithelium can be identified on histologic examination (126,127) or when a patient coughs up clumps of desquamated epithelial cells (creola bodies). Bronchial mucus contains eosinophils, which may be observed in expectorated sputum. Charcot–Leyden crystals (lysophospholipase) are derived from eosinophils and appear as dipyramidal hexagons or needles in sputum. Viscid mucus plugs, when expectorated, can form a cast of the bronchi and are called Curschmann's spirals.

In clinically active asthma, mucus hypersecretion is reduced or eliminated after treatment with systemic and then ICS. Mucus from patients with asthma has tightly bound glycoprotein and oligosaccharide, compared with that from patients with chronic bronchitis (128). Viscoelastic features of bronchial mucus in patients with asthma are associated with the presence of gel-forming glycoproteins, MUC5B and MUC5AC (129). One or both of these glycoproteins can be demonstrated on staining of mucus plugs from patients dying from asthma (129). IL-13 *in vitro* is a potent stimulus for MUC5AC (129).

The bronchial mucosa is edematous, as is the submucosa, and both are infiltrated with mast cells, activated eosinophils, and $CD4^+$ T_H2 lymphocytes (3,4). Neutrophils can be a manifestation of severe persistent asthma (3,4,120). Macrophages and epithelium both amplify the inflammatory responses of asthma (3,4). Venous dilation, plasma leakage, and proliferation of new vessels occur along with the cellular infiltration and production of tenacious mucus (3,4,127). In addition to its presence on mast cells, basophils, eosinophils, dendritic cells (monocytes and macrophages), and platelets, IgE has been identified in bronchial glands, epithelium, and basement membrane.

The mechanism of bronchial hyperresponsiveness in asthma is unknown but

is perhaps the central abnormality physiologically. Bronchial hyperresponsiveness occurs in patients with asthma to agonists, such as histamine, methacholine, mannitol, LTD_4, allergens, platelet-activating factor (PAF), PGD_2 (short-lived response), and adenosine monophosphate. Bronchial hyperresponsiveness is sensitive for asthma if one considers a maximum dose of methacholine of 8 mg/mL, which is necessary to cause a decline in FEV_1 of 20%. Patients with active symptomatic asthma often experience such a decline in FEV_1 when the dose of methacholine is 2 mg/mL or less. However, bronchial hyperresponsiveness is not specific for asthma because it occurs in patients who have disease other than asthma (Table 19.2).

TABLE 19.2 CONDITIONS OF PATIENTS THAT MAY DEMONSTRATE BRONCHIAL HYPERRESPONSIVENESS

1. After a viral upper respiratory infection for 6 wk in nonasthma patients
2. In absence of changes in FEV_1 in patients with asthma
3. In chronic bronchitis
4. In left ventricular failure
5. In allergic rhinitis in absence of asthma
6. In apparently normal subjects
7. In subjects exposed to irritants
8. In smokers
9. In some normal infants
10. In first-degree relatives of asthma patients
11. In sarcoidosis
12. In patients with quadriplegia or high paraplegia (lesions T1–T6)

FEV_1, forced expiratory volume in 1 second.

Bronchial hyperresponsiveness is measured physiologically by reductions in expiratory flow rates, FEV_1, or decreases in specific conductance. Nevertheless, hyperresponsiveness consists of bronchoconstriction, hypersecretion, and hyperemia (mucosal edema). It has been easier to measure airway caliber by changes in FEV_1 than to measure changes in bronchial gland secretion, cellular infiltration, or blood vessels (dilation and increased permeability) that also contribute to hyperresponsiveness and cause airways obstruction. Indeed, there

has yet to be an "inflammamometer" for asthma. The bronchial responsiveness detected after challenge with histamine or methacholine measures bronchial sensitivity or ease of bronchoconstriction (123). As stated, an additional finding in some patients with asthma is excessive bronchoconstriction, which can be attributable to associated increases in RV and, possibly, more rapid clinical deterioration (123).

Often, on opening the thorax of a patient who has died from status asthmaticus, the lungs are hyperinflated and do not collapse (Fig. 19.1). Mucus plugging and obstruction of bronchi and bronchioles are present. In some cases, complicating factors, such as atelectasis or acute pneumonia, are identified. On histologic examination, there is a patchy loss of bronchial epithelium with desquamation and denudation of mucosal epithelium. Eosinophils are present in areas of absent epithelium, and immunologic staining has revealed evidence of eosinophil MBP at sites of bronchial epithelium desquamation. Activated (EG2-positive) eosinophils are present in the mucosa, submucosa, and connective tissue. Other histologic findings include hyperplasia of bronchial mucus glands, bronchial mucosal edema, smooth muscle hypertrophy, and basement membrane thickening (Fig. 19.2). The latter occurs from the remodeling process from collagen deposition (types I, III, and IV), Ig deposition, and cellular infiltrates as evidence of inflammation. The mucus plugs typically contain eosinophils and are very tenacious. Occasionally, bronchial epithelium is denuded, but histologic studies do not identify eosinophils. In some cases, neutrophils have been present (113). Similarly, although many autopsy examinations reveal the classic pattern of mucus plugging of large and smaller bronchi and bronchioles leading to mucus suffocation or asphyxia as the terminal asthmatic event, some autopsies reveal empty bronchi (113,114,124,127). Eosinophils have been identified in such cases in airways or in basement membranes, but a gross mechanical explanation, analogous to mucus suffocation, is not present. A third morphologic pattern of patients dying from asthma is that of mild-to-moderate mucus plugging without apparent mucus suffocation.
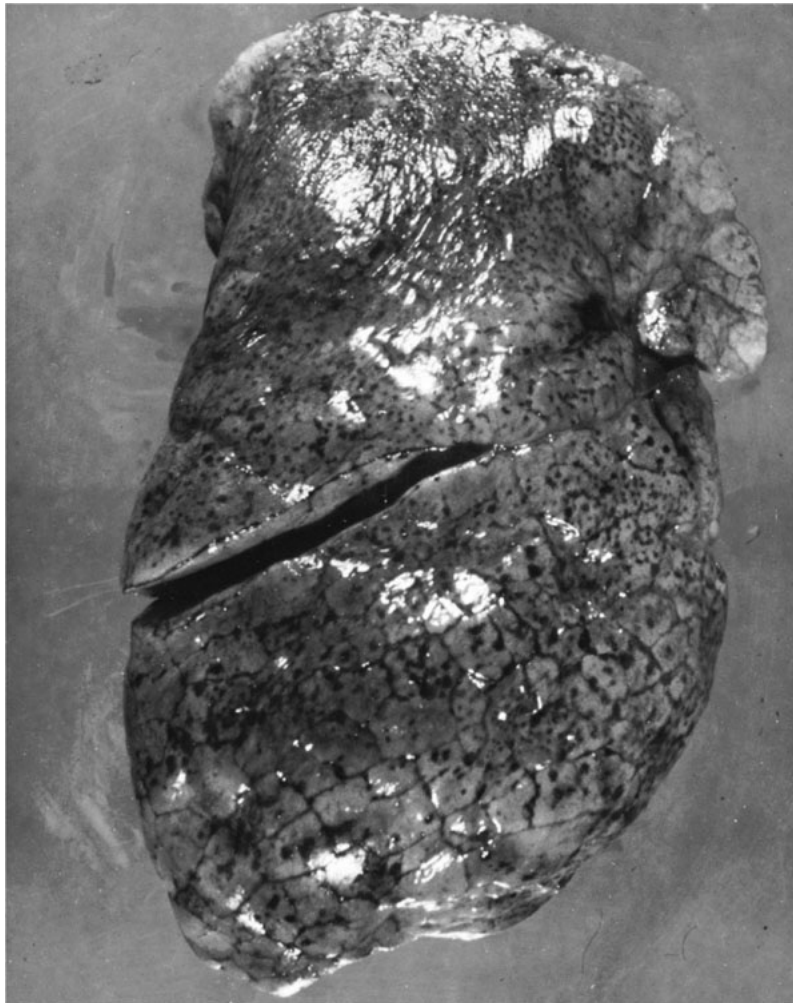
■ **FIGURE 19.1** Distended lung of patient who died in acute severe asthma (status asthmaticus).
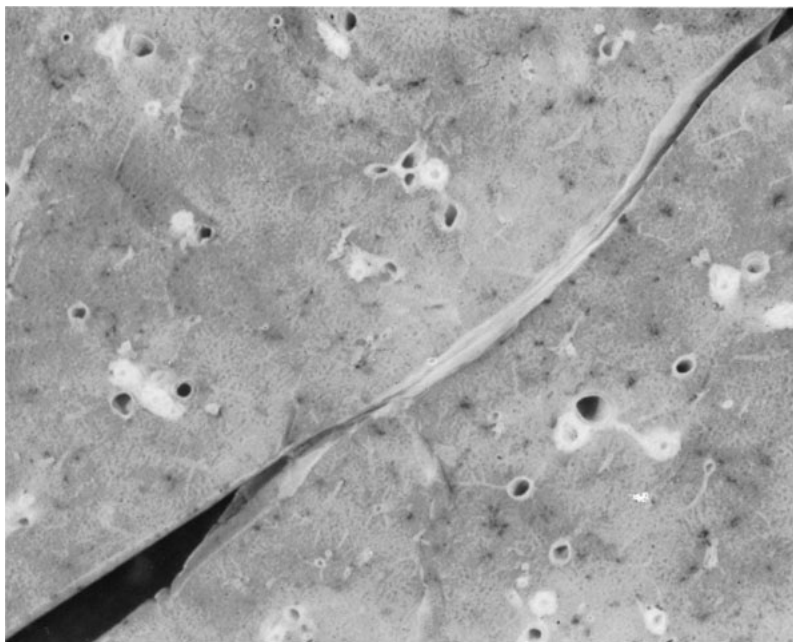
■ **FIGURE 19.2** Close-up view of pulmonary parenchyma in a case of acute

severe asthma. Bronchi are dilated and thickened.

Some patients dying from asthma have evidence of myocardial contraction band necrosis, which is different from myocardial necrosis associated with infarction. Contraction bands are present in necrotic myocardial smooth muscle cell bands in asthma, and curiously, the cells are thought to die in tetanic contraction, whereas in cases of fatal myocardial infarction, cells die in relaxation. (It should be kept in mind that some patients with asthma, die suddenly from other causes, such as substance abuse) (114).

In patients who experience acute severe asthma but do not die from it, it can be expected that when the patient presents with an FEV_1 of 50% of predicted value, there may be a 10-fold increase in inspiratory muscle work. Pleural pressure becomes more negative, so that as inspiration occurs, the patient is able to apply sufficient radial traction on the airways to maintain their patency. Air can get in more easily than it can be expired, which results in progressively breathing at higher and higher lung volumes. The RV increases several-fold, and FRC expands as well. Expiratory flow rates decrease in large and small airways. The lung hyperinflation is not distributed evenly, and some areas of the lung have a high or low ventilation-perfusion (V/Q) ratio. Overall, the hypoxemia that results from acute severe asthma occurs from reduced V/Q, not from shunting of blood. The lung hyperinflation also results in "dynamic auto–positive end-expiratory pressure" because the patient attempts to maintain airway caliber by applying some endogenous positive airway pressure.

There is no evidence of chest wall (inspiratory muscle) weakness in patients with asthma. Nevertheless, some patients who have received prolonged courses of daily or twice-daily prednisone or who have been mechanically ventilated with muscle relaxants and corticosteroids can be those who have respiratory muscle fatigue.

After successful treatment of an attack of acute severe asthma, the increases in lung volume may remain present for 6 weeks. The changes are primarily in RV and FRC. Small airways may remain obstructed for weeks or months; in some patients, they do not become normal again. At the same time, it can be expected that the patient has no sensation of dyspnea within 1 week of treatment of acute severe asthma despite continued increases in RV and reduced small airways caliber. This divergence between symptom recognition in asthma and physiologic measurements has been demonstrated in ambulatory patients who did not have acute severe asthma (status asthmaticus) (130). When patients with an FEV_1 percentage of 60% were studied, 31% overestimated and 17%

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underestimated the extent of airway obstruction (130). Some patients reported fewer symptoms despite no improvement in FEV_1 or peak expiratory flow rate (PEFR). The reduction in trapped gas in the lung can result in symptom reduction even without improvement in expiratory flow rates.

Asthma pathophysiology includes poor or impaired symptom perception in some patients and in management of asthma, increased symptom perception in others (131–133). There may be poor sensitivity or discrimination (recognizing improvement or worsening status). Dyspnea has been classified into (a) inspiratory difficulty, (b) chest tightness, (c) unsatisfied inspiration, or (d) work (134,135). Table 19.3 presents factors that alter the perception of dyspnea in asthma. As the exacerbation of asthma becomes worse, the reduction in inspiratory capacity is associated with increases in FRC (hyperinflation) and increasing dyspnea (134,135).

TABLE 19.3 FACTORS THAT AFFECT THE SENSATION OF DYSPNEA IN ASTHMA

1. Age
2. Gender
3. Temporal adaptation to airway obstruction
4. Severity of asthma
5. Extent of decline in FEV_1[a]
6. Personality (high anxiety, low anxiousness, etc.)
7. Psychologic profile
8. Medications
9. Concurrent pulmonary, cardiac or neurologic conditions
10. Obesity

[a]For patients who have mild dyspnea at a reduction of 20% of FEV_1, the dyspnea would be much more noticeable with a 50% decline of FEV_1. Some "poor perceiver" patients have no appreciation of dyspnea when the FEV_1 has decreased by 50%.

FEV1, forced expiratory volume in 1 second.

CONTROL OF AIRWAY TONE

The patency of bronchi and bronchioles is a function of multiple factors. There is the overriding that loss of airway distensibility will less elastic recoil pressures

(136). Bronchomotor patency is affected by mediators secreted by mast cells, the autonomic nervous system, the NANC nervous system, circulating humoral substances, the respiratory epithelium, smooth muscle cells, and effects of cellular infiltration and glandular secretions (Table 19.4). Even this list is oversimplified because asthma must be considered a very complex condition in terms of airway caliber and tone.

Mediator release caused by mast cell activation results in acute and late bronchial smooth muscle contraction, cellular infiltration, and mucus production. Autonomic nervous stimulation contributes through vagal stimulation. The neurotransmitter for postganglionic parasympathetic nerves is acetylcholine, which causes smooth muscle contraction. Norepinephrine is the neurotransmitter for postganglionic sympathetic nerves. However, there appears to be little if any significant smooth muscle relaxation through stimulation of postganglionic sympathetic nerves. Exogenously administered epinephrine can produce smooth muscle relaxation. Circulating endogenous epinephrine apparently does not serve to produce relaxation of smooth muscles. Sensory nerves in the respiratory epithelium are stimulated and lead to release of a host of neuropeptides that may be potent bronchoconstrictors or bronchodilators. Respiratory epithelium itself may contain bronchi-relaxing factors that may become unavailable when epithelium is denuded. Table 19.4 list some chemical mediators derived from mast cells and cytokines and neuropeptides that may contribute to pathogenesis of asthma.

Although much attention has been directed at understanding the contribution of IgE and mast cell activation in asthma, triggering or actual regulation of some of the allergic inflammation of asthma may occur because of other cells in lungs of patients. Low-affinity IgE receptors (Fcε RII) are present on macrophages, eosinophils, monocytes, B lymphocytes, and platelets. These cells, as well as mast cells in the bronchial mucosa or lumen, can be activated in the absence of classic IgE-mediated asthma.

Bronchial biopsy specimens from patients with asthma demonstrate mucosal mast cells in various stages of activation in patients with and without symptoms. Mast cell hyperreleasability may occur in asthma in that bronchoalveolar mast cells recovered during lavage contain and release greater quantities of histamine when stimulated by allergen or anti-IgE *in vitro*.

Eosinophils contribute to pro-inflammatory effects by secretion of injurious cell products, such as MBP, that can result in bronchial epithelial denudation, exposing sensory nerves, and leading to smooth muscle contraction. Eosinophils

cause eosinophil and neutrophil chemotaxis, which produces positive feedback in terms of leukotriene and PAF production from attracted and newly activated eosinophils. The latter can be demonstrated by activation markers such as EG2 and reduced density on centrifugation, the so-called hypodense eosinophils.

On a cellular level, the control of airway tone is influenced by even more fundamental factors, including IL-1, IL-2, IL-3, IL-4, IL-6, IL-10, IL-12, IL-16, IFNγ, among others, that influence lymphocyte development and proliferation. IL-3 and IL-5 are eosinophil growth factors. IL-8, detected in bronchial epithelium, binds to secretory IgA and serves to chemoattract eosinophils that generate PAF and LTC_4. IL-8 is also a potent chemotactic substance for neutrophils.

TABLE 19.4 SELECTED MAST CELL MEDIATORS AND CYTOKINES AND THEIR PROPOSED ACTIONS IN ASTHMA

MEDIATOR	PREFORMED	NEWLY SYNTHESIZED	ACTIONS
Histamine	+		Smooth muscle contraction (H_1 and via vagus); increased vascular permeability; vasodilator; mucus production (H_2)
Tryptase	+		Degrades vasoactive intestinal polypeptide; cleaves kininogen to form bradykinin, complement C3
Eosinophil chemotactic factor	+		Eosinophil chemoattractant
Neutrophil chemotactic factor	+		Neutrophil chemoattractant
Peroxidase	+		Inactivates leukotrienes
Bradykinin		+	Smooth muscle

		contraction
Leukotriene D_4 (generated from leukotriene C_4)	+	Smooth muscle contraction; increases vascular permeability, mucus secretion
Prostaglandin D_2, $F_{2\alpha}$	+	Smooth muscle contraction; increases vascular permeability, mucus secretion
Platelet-activating factor	+	Smooth muscle contraction; increases vascular permeability, neutrophil and eosinophil chemoattractant; aggregates platelets; sensitizes airways to the agonists
Leukotriene B_4	+	Neutrophil and eosinophil chemoattractant
Interleukin-3 (IL-3)	+	Eosinophil growth factor and chemoattractant, stem cell growth, mast cell growth
IL-5	+	Eosinophil growth factor and chemoattractant
Granulocyte-macrophage colony-stimulating factor	+	Eosinophil growth factor and chemoattractant
IL-1	+	Cytokine production; B-cell differentiation and proliferation
IL-2	+	Proliferation of T cells

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IL-4		+	Growth of B cells; class switching from immunoglobulin M (IgM) to IgE production; increases VCAM on endothelium. Favors T_H2 phenotype of CD4$^+$ T cells
Tumor necrosis factor-α		+	Activation of macrophages with increased major histocompatibility complex (MHC) molecules (increased antigen presentation)
Interferon-γ		+	Increased MHC molecules on macrophages, antiviral
IL-9	+		Growth and survival of mast cells and CD4$^+$ T cells; mucus production
IL-25	+		Supports polarization of T_H2 responses; production of IL-8
IL-33	+		Supports polarization of T_H2 responses
TSLP	+		Supports polarization of T_H2 responses; activates epidermal Langerhans cells

TSLP, thymic stromal lymphopoietin; VCAM, vascular cell adhesion molecule.

During an acute attack of asthma, there is an increase in inspiratory efforts, which apply greater radial traction to airways. Patients with asthma have great ability to generate increases in inspiratory pressures. Unfortunately, patients who have experienced nearly fatal attacks of asthma have blunted perception of dyspnea (137) and impaired ventilatory responses to hypoxia (138). Thus, as the airways obstruction worsens, trapped air in the lung increases. The patient breathes at higher lung volumes and more inefficiently just to maintain an effective vital capacity. Then, as the severity of the attack of asthma intensifies, the FVC will be reduced so that it approaches the tidal breathing. Respiratory acidosis, failure, or arrest can be expected.

When patients with persistent severe asthma were divided into eosinophil-positive (and macrophage-positive) and eosinophil-negative categories based on results on bronchial biopsy findings (139), physiologic differences were identified. Both subgroups of patients were prednisone dependent (average, 28 mg daily) and had asthma for about 20 years (139). The RV measurements were about 200% of predicted, and FEV_1 percentage was 56% of predicted in eosinophil-positive and 42% of predicted in eosinophil-negative patients (139). The ratio of the FVC to *slow* vital capacity was 88%, indicating more airway collapsibility in eosinophil-positive patients, compared with 97% in eosinophil-negative patients. Perhaps the former patients who had somewhat higher FEV_1 percentages had more loss of elastic recoil in their lungs, so that their airways collapsed more easily (139). On biopsy assessments, sub-basement membrane thickening was higher in these eosinophil-predominant patients than in eosinophil-negative patients. These findings were associated with eosinophil-predominant patients with severe asthma having an increased number of CD3^{+} lymphocytes and activated eosinophils (EG2^{+}) in biopsy samples and an increased quantity of β-tryptase in BAL. It is likely that the cellular inflammation and cell products participate in control or perturbation of airway tone, and continued investigations of the many aspects of allergic inflammation should help clarify this difficult issue.

CLINICAL OVERVIEW

Clinical Manifestations

Asthma results in coughing, wheezing, dyspnea, sputum production, and shortness of breath. Symptoms vary from patient to patient and within the individual patient depending on the activity of asthma. Some patients experience mild, nonproductive coughing after exercising or exposure to cold air or odors as

examples of transient mild bronchoconstriction. The combination of coughing and wheezing with dyspnea is common in patients who have a sudden moderate-to-severe episode (such as might occur within 3 hours after aspirin ingestion in an aspirin-intolerant patient). Symptoms of asthma may be sporadic and are often present on a nocturnal basis. Some patients with asthma present with a persistent nonproductive cough as a main symptom of asthma (4,6). Typically, the cough has occurred on a daily basis and may awaken the patient at night. Repetitive spasms of cough from asthma are refractory to treatment with expectorants, antibiotics, antitussives, and opioids. The patient likely may respond to an inhaled β_2-adrenergic agonist; if that is unsuccessful, ICS or the combination may work. At times, oral corticosteroids are necessary to stop the coughing and are very useful as a diagnostic therapeutic trial (4,6). Pulmonary physiologic studies usually reveal large airway obstruction, as illustrated by reductions in FEV_1 with preservation of forced expiratory flow, midexpiratory phase ($FEF_{25\%-75\%}$), or small airways function. The latter may be reduced in patients with this cough variant form of asthma. Conversely, some patients present with isolated dyspnea as a manifestation of asthma. Some of these patients have small airways obstruction with preservation of function of larger airways. The recognition of variant forms of asthma emphasizes that not all patients with asthma have detectable wheezing on auscultation. The medical history is important, as is a diagnostic-therapeutic trial with antiasthma medications. Pulmonary physiologic abnormalities, such as reduced FEV_1 that responds to therapy, or bronchial hyperresponsiveness to methacholine (PC_{20} < 8 mg/mL) can provide additional supportive data.

During an acute, moderately severe episode of asthma or in longer term ineffectively controlled asthma, patients typically produce clear, yellow, or green sputum that can be viscid. The sputum contains eosinophils that support the diagnosis of asthma. If measured, expired nitric oxide concentrations will be elevated. Because either polymorphonuclear leukocytes or eosinophils can cause the sputum to be discolored, it is inappropriate to consider such sputum as evidence of a secondary bacterial infection. Patients with nonallergic asthma also produce eosinophil-laden sputum. An occasional patient with asthma presents with cough syncope, a respiratory arrest that is perceived as anaphylaxis, chest pain, pneumomediastinum, pneumothorax, or with symptoms of chronic bronchitis or bronchiectasis.

The physical examination may consist of no coughing or wheezing if the patient has stable persistent asthma or if there has not been a recent episode of

intermittent asthma. Certainly, patients with variant asthma may not have wheezing or other supportive evidence of asthma. Usually, wheezing is present in other patients and can be associated with reduced expiratory flow rates. A smaller number of patients always have wheezing on even tidal breathing, not just with a forced expiratory maneuver. Such patients may not report symptoms and may or may not have expiratory airflow obstruction when FVC and FEV_1 are measured. The physical examination must be interpreted in view of the patient's clinical symptoms and supplemental tests, such as the chest radiograph or pulmonary function tests. There may be a surprising lack of correlation in some ambulatory patients between symptoms and objective evidence of asthma (physical findings and spirometric values). (Attempts at using a biomarker such as eNO have (140) and have not (141) been helpful as a prospective, noninvasive marker to assist in management of patients with asthma. Similarly, studies have supported and not supported serial use of sputum eosinophils).

An additional physical finding in patients with asthma is repetitive coughing on inspiration. Although not specific for asthma, it is frequently present in unstable patients. In normal patients, maximal inspiration to total lung capacity results in reduced airway resistance, whereas in patients with asthma, increased resistance occurs with a maximal inspiration. Coughing spasms can be precipitated in patients who otherwise may not be heard to wheeze. This finding is transient and, after effective therapy, will not occur. The patient with a very severe episode of asthma may be found to have pulsus paradoxus and use of accessory muscles of respiration. Such findings correlate with an FEV_1 of less than 1.0 L and air trapping as manifested by hyperinflation of the FRC and RV. The most critically ill patients have markedly reduced tidal volumes, and their maximal ventilatory efforts are not much higher than their efforts during tidal breathing. A silent chest with absence of or greatly reduced breath sounds indicates likely alveolar hypoventilation (normal or elevated arterial PCO_2) and hypoxemia. Such patients may require intubation or, in most cases, admission to the intensive care unit. Great difficulty in speaking more than a half sentence before needing another inspiration is likely present in such patients. Persistent asthma may be occurring in patients who have concurrent gastroesophageal reflux disease (GERD), rhinosinusitis, allergic or nonallergic rhinitis, or an upper respiratory infection, all of which can cause a troublesome cough or worsen ongoing asthma.

Radiographic and Laboratory Studies

In about 90% of patients, the presentation of chest radiograph is considered within normal limits (142). The most frequently found abnormality is hyperinflation. The diaphragm is flattened, and there may be an increase in the anteroposterior diameter and retrosternal air space. The chest radiograph is indicated because it is necessary to exclude other conditions that mimic asthma and to search for complications of asthma. Congestive heart failure (CHF), COPD, pneumonia, sarcoidosis, and neoplasms are just some other explanations for acute wheezing dyspnea that may mimic or coexist with asthma. Asthma complications include atelectasis as a result of mucus obstruction of bronchi, mucoid impaction of bronchi (often indicative of allergic bronchopulmonary aspergillosis [ABPA]), pneumomediastinum, and pneumothorax. Atelectasis often involves the middle lobe, which may collapse. The presence of pneumomediastinum or pneumothorax may have associated subcutaneous emphysema with crepitus on palpation of the neck, supraclavicular areas, or face (Fig. 19.3). Sharp pain in the neck or shoulders should be a clue to the presence of a pneumomediastinum in acute severe asthma (status asthmaticus).

Depending on the patients examined, abnormal findings on sinus computed tomography (CT) examination may be frequent. Some findings may include air–fluid levels, indicative of infection; mucoperiosteal thickening, which is consistent with current or previous infection; and opacification of a sinus or presence of nasal polyps (see Chapters 10 and 12). Clinical research studies of acutely ill patients with asthma have been carried out with V/Q scans. These procedures are not indicated in most cases and, in the markedly hypoxemic patient, may be harmful because the technetium-labeled albumin macrospheres injected for the perfusion scan can lower arterial PO_2. Nevertheless, ventilation of the lung is uneven (142). Perfusion scans reveal abnormalities such that there may or may not be matched V/Q inequalities. In some patients, the V/Q in the superior portions of the lungs has declined from its otherwise high value (142). The explanation for such a finding is increased perfusion of upper lobes presumably from reduced resistance relative to lower lobes that receive most of the pulmonary blood flow. Little evidence for shunting exists (142). Of note, even bronchoprovocation challenge with allergen results in 20% increases in V/Q with associated evidence of gas trapping.
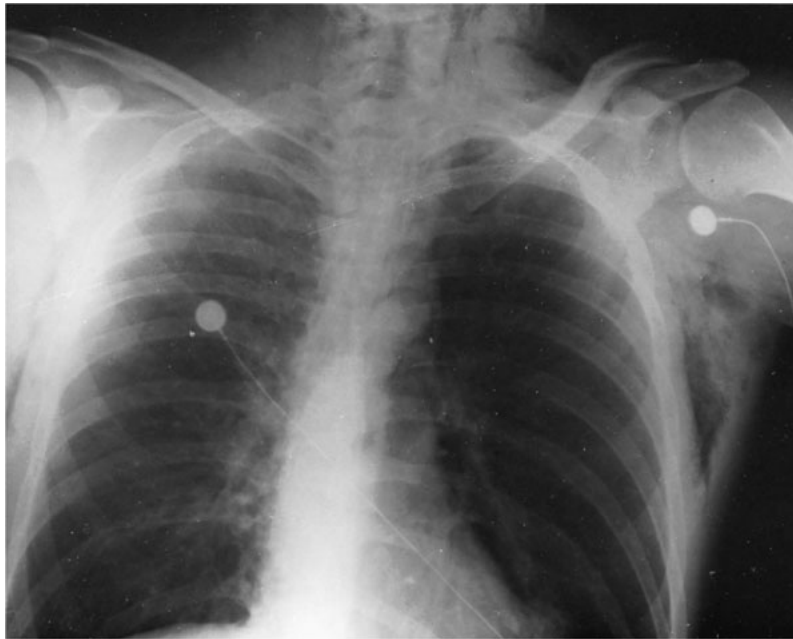
■ **FIGURE 19.3** Anteroposterior view of the chest of a 41-year-old woman demonstrates hyperinflation of both lungs, with pneumomediastinum and subcutaneous emphysema.

Pulmonary emboli typically do not complicate episodes of acute asthma, but when a pulmonary embolus is suspected, spiral CT examination of the lung may provide the characteristic findings.

In the assessment of the emergency department patient with acute severe wheezing dyspnea, the measurement of arterial PO_2, PCO_2, and pH can be invaluable. Although hypoxemia is a frequent and expected finding and is identified by measuring the pulse oximetry, the PCO_2 provides information on the effectiveness of alveolar ventilation. This latter status will not be assessed if just oxygen saturation is determined. The PCO_2 should be decreased initially during the hyperventilation stage of acute asthma. A normal or an elevated PCO_2 is evidence of alveolar hypoventilation and may be associated with subsequent need for intubation to try to prevent a fatal outcome.

Pulmonary function measurements can help to establish patient status. However, such measurements must be correlated with the physical examination. In the emergency department or ambulatory setting, many physicians determine spirometric values for expiratory flow rates with either PEFR or FEV_1. These tests are effort dependent, and patients with acute symptoms may be unable to perform the maneuver satisfactorily. This finding could be from severe obstruction or patient inability or unwillingness to perform the maneuver appropriately. When properly performed, spirometric measurements can be of

significant clinical utility in assessing patient status. For example, as a rule, patients presenting with spirometric determinations of 20% to 25% of predicted value should receive immediate and intensive therapy. Frequent measurements of peak expiratory flow rate (PEFR) or FEV_1 in ambulatory patients can establish a range of baseline values for day and night. Declines of more than 20% from usual low recordings or wide swings in PEFR (such as from a best of 400 to 300 L/minute) can alert the patient to the need for more intensive pharmacologic therapy. Nevertheless, such measurements can be insensitive in some patients. Pulmonary physiologic values such as PEFR and FEV_1 have demonstrated value in clinical research studies, such as in documenting a 12% increase in expiratory flow rates after bronchodilator. Such a response (including a 200-mL increase in FEV_1) meets criteria for a bronchodilator response (3). Similarly, in testing for bronchial hyperresponsiveness, a 20% decline in FEV_1 is a goal during incremental administration of methacholine or histamine.

Some patients may benefit from measuring PEFR daily at home (1–4). Unfortunately, some patients do not continue to measure this PEFR or may fabricate results. Other patients manipulate spirometric measurements to make a convincing case for occupational asthma. Thus, the physician must correlate pulmonary physiologic values with the clinical assessment. A complete set of pulmonary function tests should be obtained in other situations, such as in assessing the degree of reversible versus nonreversible obstruction in patients with heavy smoking histories. The diffusing capacity for carbon monoxide (DLCO) is *reduced* in the COPD patient but *normal or elevated* in the patient with asthma. Such tests should be obtained after 2 to 4 weeks of intensive therapy to determine what degree of reversibility exists. In acutely ill patients with asthma, the DLCO may be reduced. Thus, its usefulness in differentiating COPD from asthma will be obscured if the wrong time is chosen to obtain this test. Flow-volume loops will demonstrate intrathoracic obstruction in patients with asthma (1–4) or extrathoracic obstruction in those with vocal cord dysfunction (VCD) (143,144) (Fig. 19.4).

The complete blood count should be obtained in the emergency setting. First, the hemoglobin and hematocrit provide status regarding anemia, which, if associated with hypoxemia, can compromise oxygen delivery to tissues. Conversely, an elevated hematocrit is consistent with hemoconcentration such as occurs from dehydration or polycythemia. The latter does not occur in asthma in the absence of other conditions. The white blood count may be elevated from infection or systemic corticosteroids, the mechanism of which includes

demargination and release from bone marrow. In the absence of prior systemic corticosteroids, the acutely ill patient with allergic or nonallergic asthma often has peripheral blood eosinophilia. For best accuracy, an absolute eosinophil count is required. The absolute eosinophil count in the absence of administration of systemic cortiocosteroids can be useful if the patient will be a candidate for immunomodulator therapy (mepolizumab or reslizumab). The presence of eosinophilia in patients receiving long-term systemic corticosteroids should suggest nonadherence or, possibly, rare conditions, such as eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss syndrome), ABPA, or chronic eosinophilic pneumonia. Usually, the eosinophilia in acute asthma does not exceed 10% to 20% of the differential. (Some patients with both asthma and atopic dermatitis have persistently elevated absolute eosinophil counts in the absence of idiopathic hyperesoinophilic syndrome or other conditions). Much higher values should suggest an alternative diagnosis (see Chapter 35).
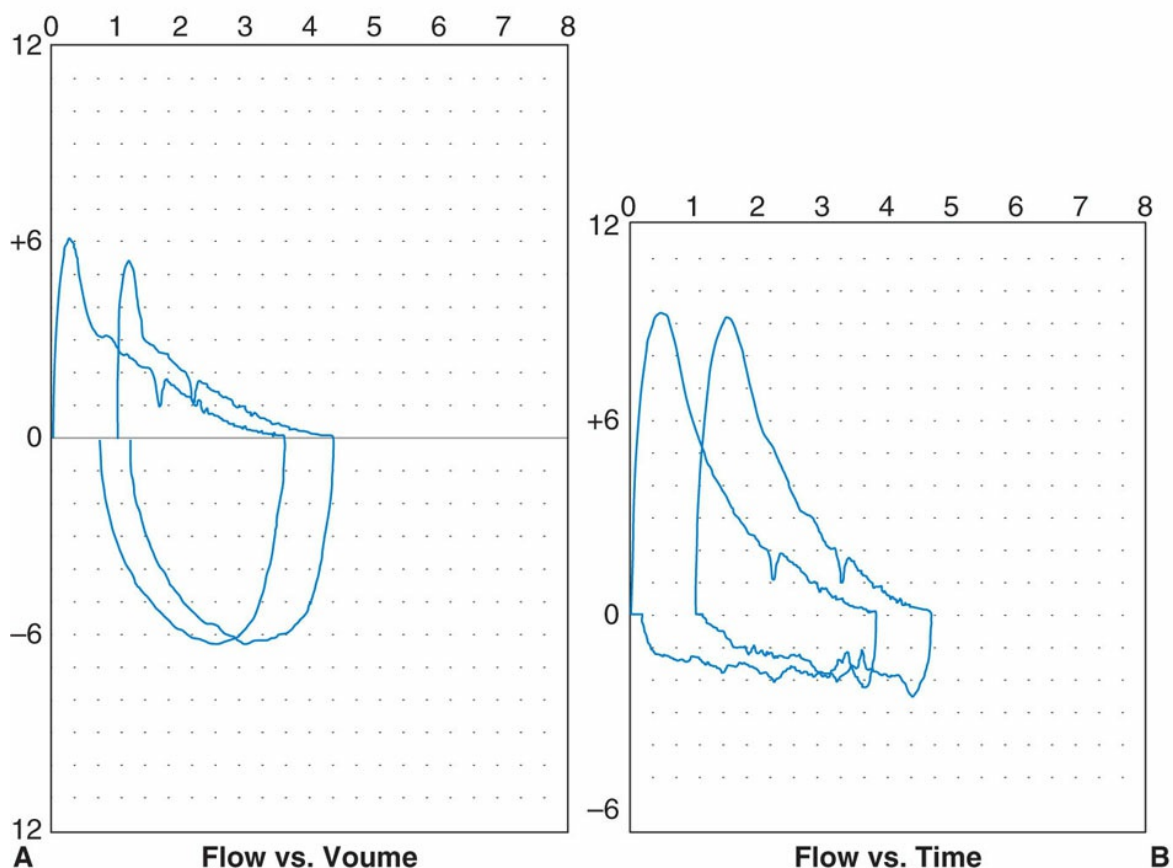
■ **FIGURE 19.4 A:** A 46-year-old man with persistent asthma since childhood. He had been taking prednisone, 60 mg daily for 6 weeks; salmeterol, 2 puffs twice a day; and budesonide, 800 µg twice a day. He had mild expiratory wheezes on examination. The pattern is that of intrathoracic obstruction from asthma. The forced vital capacity (FVC) was 3.6 L (72%), and the forced

expiratory volume in 1 second (FEV_1) was 2.3 L (62%). The FEV_1 percentage was 64%. The forced expiratory flow, mid-expiratory phase ($FEF_{25\%-75\%}$) was 1.36 L/second (36%). The inspiratory loop is not altered. **B:** A 47-year-old man with adult-onset asthma and intermittent sinusitis, nonallergic rhinitis, and gastroesophageal reflux disease. Medications included prednisone, 35 mg on alternate days; budesonide, 800 µg twice a day; salmeterol, 2 puffs twice a day; omeprazole, 40 mg daily; fexofenadine, 60 mg twice daily; and triamcinolone nasal spray. He had mild end-expiratory wheezes and a hoarse voice. No stridor was present. The FVC was 3.9 L (78%), the FEV_1 was 2.9 L (77%), and the FEV_1 percentage was 74%. The $FEF_{25\%-75\%}$ was 2 L/second (56%). The inspiratory loop is truncated, consistent with vocal cord dysfunction.

Sputum examination reveals eosinophils, eosinophils plus polymorphonuclear leukocytes (asthma and purulent bronchitis or bacterial pneumonia), or neutrophils. In mild asthma, no sputum is produced. In severely ill patients with asthma, the sputum is thick, tenacious, and yellow or green. MBP from eosinophils has been identified in such sputum. Dipyramidal hexagons from eosinophil cytoplasm may be identified and are called Charcot–Leydon crystals. These crystals contain lysophospholipase. Curschmann spirals are expectorated yellow or clear mucus threads that are remnants or casts of small bronchi. Expectorated ciliated and nonciliated bronchial epithelial cells can also be identified that emphasize the patchy loss of bronchial epithelium in asthma.

Serum electrolyte abnormalities may be present and should be anticipated in the patient presenting to the emergency department. Recent use of oral corticosteroids can lower the potassium concentration (as can β_2-adrenergic agonists) and cause a metabolic alkalosis. Oral corticosteroids may raise the blood glucose in some patients, as can systemic administration of β_2-adrenergic agonists. Elevations of atrial natriuretic peptide and antidiuretic hormone can occur in acute asthma or COPD (145). Clinically, few patients have large declines of serum sodium. Because intravenous fluids will be administered, it is necessary to determine the current status of electrolytes and serum chemistry values. After prolonged high-dose corticosteroids, hypomagnesemia or hypophosphatemia may occur.

Rarely, a patient younger than 30 years of age may be thought to have asthma when the underlying condition is α_1-antitrypsin deficiency. More commonly, patients with wheezing dyspnea have asthma and cystic fibrosis. The sweat chloride should be elevated markedly in such patients. A properly performed

sweat chloride test is essential, as is proper performance of genetic analysis and pancreatic function.

In the outpatient management of asthma, determination of the presence or absence of antiallergen IgE is of value. For decades, skin testing for immediate cutaneous reactivity has been the most sensitive and specific method. Some physicians prefer *in vitro* tests. One cannot emphasize enough the need for high-quality control for both skin testing and *in vitro* testing. Both tests are subject to misinterpretation. The experienced physician should use either method of demonstration of antiallergen IgE as adjunctive to, rather than a substitute for, the narrative history of asthma. More patients have immediate cutaneous reactivity or detectable *in vitro* IgE than have asthma that correlates with exposure to the specific allergen.

Complications

Complications from asthma include death, adverse effects of hypoxemia or respiratory failure on other organ systems, growth retardation in children, pneumothorax or pneumomediastinum, rib fractures from severe coughing, cough syncope, and adverse effects of medications or therapeutic modalities used to treat asthma. Some patients develop psychologic abnormalities because of the burden of a chronic illness such as asthma. Ineffectively treated asthma in children can result in chest wall abnormalities, such as "pigeon chest," because of sustained hyperinflation of the chest. Further, the annual rate of decline of FEV_1 is increased; for example, it may be 38 mL/year in patients with asthma, compared with 22 mL/year in patients without asthma (146). The loss of FEV_1 can be considered from the perspective of severe exacerbations: no exacerbation, 13.6 mL/year; 1 exacerbation, 41.3 mL/year; 2 or more exacerbations, 58.3 mL/year (147).

In general, long-term asthma does not result in severe, irreversible obstructive lung disease. However, some patients with childhood onset of asthma may have reduced lung growth without any recovery with aging or normal lung growth in childhood/adolescence, but prematurely begin to lose the FEV_1 in their early 20s (148). However, a few patients with long-term asthma develop apparently "irreversible asthma" in the absence of cigarette smoking, α_1-antitrypsin disease, or other obvious cause (149). Usually, these patients have childhood-onset asthma and are dependent on oral corticosteroids. Intensive therapy with oral and ICS does not result in a normal FEV_1 of 80% of the predicted value because the mean FEV_1 was 57% (149). In contrast to the few patients with irreversible

asthma, patients with asthma do not become "respiratory cripples," as might occur from COPD. Nevertheless, pulmonary physiologic studies do not reveal return of parameters to the expected normal ranges. Asthma patients are not deficient in the antiproteases that can be measured, and they do not have bullous abnormalities on chest radiographs. CT demonstrates gas trapping, especially on expiration, as well as bronchial wall thickening caused by increased smooth muscle mass and elastic and collagenous tissue. Some patients with asthma have evidence of bronchial dilatation on high-resolution CT examination (150), but there are few areas of involvement in contrast to that of ABPA (see Chapter 24).

Pneumomediastinum or pneumothorax can occur in patients presenting with acute severe asthma. Neck, shoulder, or chest pain is common, and crepitations can be detected in the neck or supraclavicular fossae. Rupture of distal alveoli results in dissection of air proximally through bronchovascular bundles. The air can then travel superiorly in the mediastinum to the supraclavicular or cervical areas. At times, the air dissects to the face or into the subcutaneous areas over the thorax. Treating the patient's asthma with systemic corticosteroids is indicated to reduce the likelihood of hyperinflation and continued air leak. Unless the pneumothorax is very large, conservative treatment is effective. Otherwise, thoracostomy with tube placement is necessary.

Fatalities from asthma are unnecessary because asthma is not an inexorably fatal disease. Fatalities do occur, however, and many factors have been suggested as explanations (1–4,151,152). While some deaths from asthma are unavoidable despite appropriate medical care, a high percentage of deaths from asthma should be considered preventable. Survivors of major asthma events, such as respiratory failure or arrest, patients with pneumomediastinum or pneumothorax on two occasions, and those with repeated status asthmaticus despite oral corticosteroids have potentially fatal asthma and are at higher risk for fatality than other patients with asthma (152). The NAEPP refers to high-risk patients as near fatal asthma (1–3).

Uncontrolled asthma can lead to mucus plugging of airways and frank collapse of a lobe or whole lung segment. The middle lobe can collapse, especially in children. Repeated mucoid impactions should raise the possibility of ABPA or cystic fibrosis.

Cough syncope or cough-associated cyanosis occurs in patients whose respiratory status has deteriorated and in whom acute severe asthma or need for emergency therapy has occurred. In the setting of severe airway obstruction from asthma, during inspiration, intrathoracic pressure is negative because the patient

must generate very high negative pressures to apply radial traction on bronchi in an attempt to maintain their patency. During expiration, the patient must overcome severe airway resistance and premature airways collapse. Increases in intrathoracic pressure during expiration with severe coughing, as compared with intra-abdominal pressure, causes a decline in venous return to the right atrium. There may also be increased blood flow to the lung during a short inspiration, but that is accompanied by pooling in the pulmonary vasculature from the markedly elevated negative inspiratory pressure. There will be reduced blood flow to the left ventricle with temporary decreases in cardiac output and cerebral blood flow.

Pulsus paradoxus is present when there is greater than a 10-mm Hg decline in systolic blood pressure during inspiration. It is associated with severe airway obstruction and hyperinflation (153). The most frequent electrocardiographic findings during acute asthma are sinus tachycardia followed by right axis deviation, clockwise rotation, prominent R in lead V_1 and S in lead V_5, and tall peaked P waves consistent with cor pulmonale.

Linear growth retardation or reduced velocity of growth can occur from ineffectively controlled asthma and potentially as a complication of high-dosage ICS. Administration of oral corticosteroids is indicated to prevent repeated hospitalizations and frequent episodes of wheezing dyspnea. The child often responds with a growth spurt. Alternate-day prednisone and recommended doses of ICS do not result in growth retardation, especially when the prednisone dose is 30 mg on alternate days or less. Even high alternate-day doses in children can be tolerated reasonably well as long as episodes of acute severe asthma are prevented. In contrast, depot corticosteroids given every 2 to 3 weeks in high doses may result in growth retardation. Despite efficacy in asthma, such corticosteroid administration causes hypothalamic-pituitary-adrenal (HPA) suppression.

The use of depot corticosteroids should be considered only in the most recalcitrant children (or adults) in terms of asthma management. Ineffective parental functioning or poor compliance usually accompanies such cases in which reliable administration of prednisone and ICS is impossible. The term *malignant, potentially fatal asthma* has been suggested for such patients who are essentially impossible to manage according to guideline-based management (154). Even, when a single intramuscular injection of triamcinolone was administered to children and adolescents with severe asthma, responses can be surprisingly variable. Some 43% of patients reported reduced symptoms of

asthma, and 54% had improvement in lung function (155). The fraction of expired nitric oxide decreased in 52% of patients and sputum eosionophils decreased in 54% (155).

The overuse of short-acting β_2-adrenergic agonists (>8 inhalations/day and especially 16 inhalations/day) is a risk factor for more severe episodes of asthma and fatalities (156). There has been controversy about scheduled use of long-acting β_2-adrenergic agonists, but the data do not support harmful effects (157,158) when used *in combination* with ICS.

Psychologic Factors

Asthma has evolved from a disorder considered to be primarily psychologic to one recognized as extremely complex and of unknown etiology. Psychologic stress can cause modest reductions in expiratory flow rates such as occur while watching a terrifying movie. Laughing and crying or frank emotional upheaval, such as an argument with a family member, can result in wheezing. The diagnosis of asthma is more frequent in people who have been victims of or witnesses to trauma. Some patients require additional anti-inflammatory medication to suppress such wheezing. Usually, if the patient has stable baseline respiratory status, acute severe asthma does not result. Nevertheless, some fatal episodes of asthma have been associated with a report of a high level of emotional stress.

The patient with asthma may develop strategies to function with the burden of asthma as a chronic, disruptive, and potentially fatal disease. A variety of behavior patterns have been recognized, including (a) disease denial, with complacency or outright denial of symptoms, wishful thinking, refusal to alert the managing physician about a major change in respiratory symptoms, or personally decreasing medications; (b) using asthma for obvious secondary gain, such as to not attend school or work, or to gain compensation; (c) developing compulsive or manipulative patterns of behavior that restrict the lifestyle of the patient and family members excessively; and (d) resorting to quackery. Some patients display hateful behavior toward physicians and their office staff. Psychiatric care can be of value in some cases (see Chapter 43), but patients may refuse appropriate psychiatric referrals. The use of PEFR monitoring devices can be misleading because patients can generate or report truly inaccurate measurements. Obviously, in contrast to theories implying that wheezing dyspnea in patients with asthma was primarily psychologic, the physician must now decide how much of a patient's symptoms and signs are from asthma and

how much might be psychologic as a result of asthma. Indeed, a psychologist, psychiatrist, or social worker may help identify what the patient might lose should asthma symptoms be controlled better.

Major management problems occur when patients with asthma have also schizophrenia, delusional behavior, neurosis, depression, or bipolar disorder. Suicidal attempts are recognized from unjustified cessation of prednisone or theophylline overdosage. Repeated episodes of life-threatening acute severe asthma are difficult to avoid in the setting of untreated major psychiatric conditions (see Chapter 43). The presence of posttraumatic stress disorder and a situation of violence and abuse or serious psychiatric disease may make it difficult or impossible to achieve goals of asthma control according to national or international guidelines.

The presence of factitious asthma indicates significant psychiatric disturbance (159). Initially, there must be trust established between the patient and physician. Abrupt referral of the patient to a psychiatrist can result in an unanticipated suicidal attempt. Psychiatric care can be valuable if the patient is willing to participate in therapy. Abnormal coping styles (93), such as wishful thinking instead of active involvement, impair the quality of life, and interfere with optimal control of asthma.

CLASSIFICATION

Some descriptive types of asthma with an emphasis on etiology are listed in Table 19.5. It is helpful to categorize the type of asthma because treatment programs vary depending on the type of asthma present. Some patients have more than one type of asthma. The NAEPP Report 3 suggests assessing signs and symptoms of asthma in association with spirometry (3). Asthma severity is classified as intermittent (most of the time, implying mild asthma) or persistent (mild, moderate, or severe). In Table 19.6, a version of this classification system is presented. It can be helpful to determine that patients have "moderate persistent allergic asthma" and use the classifications from Tables 19.5 and 19.6 together when applicable.

TABLE 19.5 CLINICAL CLASSIFICATION OF ASTHMA

Allergic asthma
Nonallergic asthma

Potentially (near) fatal asthma

Malignant potentially fatal asthma

Aspirin-intolerant asthma

Occupational asthma

Exercise-induced asthma

Variant asthma

Factitious asthma

Vocal cord dysfunction and asthma

Coexistent asthma and COPD (asthma–COPD overlap)

Irreversible asthma

COPD, chronic obstructive pulmonary disease.

TABLE 19.6 NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAM ASTHMA CLASSIFICATION SYSTEM: EXPERT PANEL REPORT 3

DESIGNATION	SYMPTOMS/SHORT-ACTING β_2-ADRENERGIC AGONIST USE	NOCTURNAL AWAKENINGS	PULMONARY FUNCTION
Intermittent	≤2 d a week (not counting prophylaxis for exercise-induced bronchoconstriction)	≤2 times a month	FEV_1 > 80%; FEV_1/FVC normal; FEV_1 normal between exacerbations

Persistent (mild)	≥2 d a week but not daily/ ≥2 d a week but not daily or more than once on a given day	3–4 times a month	FEV$_1$ > 80%; FEV$_1$/FVC normal
Persistent (moderate)	Daily symptoms/daily use	>1 night/week but not nightly	FEV$_1$ > 60% but <80%; FEV$_1$/FVC reduced by 5%
Persistent (severe)	Throughout the day/several times/day	Often 7 times/wk	FEV$_1$ < 60% FEV$_1$/FVC reduced >5%

The severity increases if one of three parameters for a given severity is not met. For example, symptoms 2 days a week and nocturnal awakenings three times a month with FEV$_1$ of 70% means persistent moderate asthma

FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity.

RECOMMENDED INITIAL/ALTERNATIVE MEDICATIONS BASED ON ASTHMA SEVERITY

DESIGNATION	INITIAL	ALTERNATIVES
Intermittent	Short-acting β$_2$-adrenergic agonist prn	
Mild	Low-dose inhaled corticosteroid	Cromolyn, leukotriene receptor antagonist, nedocromil, theophylline
Moderate	Low-dose inhaled corticosteroid + long-acting β$_2$-adrenergic agonist or medium-dose inhaled corticosteroid	Low-dose inhaled corticosteroid + leukotriene receptor antagonist, leukotriene bio-synthesis inhibitor, or theophylline
Severe	Medium-dose	Medium or high-dose inhaled

corticosteroid[a] + long-acting β$_2$-adrenergic agonist	corticosteroid[a] + Leukotriene receptor antagonist, leukotriene biosynthesis inhibitor, theophylline and consider omalizumab, mepolizumab or reslizumab

For intermittent asthma or mild, moderate and severe persistent asthma, the components of patient education, environmental control and management of comorbities are recommended.

For patients with mild, moderate or severe persistent allergic asthma, allergen immunotherapy should be considered.

[a]May require initial oral corticosteroid course to stabilize

Modified from the National Heart, Lung, and Blood Institute. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda MD: National Heart, Lung and Blood Institute, National Institutes of Health, U. S. Department of Health and Human Services; 2007. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.

Asthma in children may be classified by age of onset and persistence of wheezing (see Chapter 20). Designations include "transient early wheeze" (wheezing with lower respiratory tract illnesses before age 3 years but not thereafter), "late-onset wheeze" (wheezing beginning at or after age 6 years), and "persistent wheeze" (wheeze with lower respiratory tract illnesses before age 3 years and wheeze at age 6 years) (160,161).

In adults, another approach is that of grouping of patients with asthma into clusters using prespecified variables, including induced sputum eosinophil numbers (162). For example, some patients are classified as "concordant disease" because there is a match between symptoms and eosinophilic inflammation, whereas others are either "discordant symptoms" (excessive symptoms with little sputum eosinophilia that could characterize obese subjects or hypervigilant people) or "discordant inflammation" (few symptoms but high levels of sputum eosinophilia) (162).

A nuanced approach is the use of endotypes or distinct subtypes of asthma as opposed to phenotypes or observed characteristics (allergic or nonallergic) (163). Endotypes imply particular pathophysiology and examples include ABPA, aspirin-exacerbated respiratory disease, late-onset severe, neutrophilic asthma, and asthma predictive index positive asthma in children (163). A patient whose asthma can be classified as an endotype will also have observable characteristics (phenotypes) of asthma, such as obesity, good adherence, and poor perceiver.

Allergic Asthma

Allergic asthma is caused by inhalation of allergen that interacts with IgE present in high-affinity receptors (Fcɛ RI) on bronchial mucosal mast cells. Twenty-four hours after allergen bronchoprovocation challenge, bone marrow examination demonstrates increased numbers of eosinophil/basophil progenitor cells and classic (immunogenic antigen presenting) dendritic cells (164,165). These cells have been identified in both early responders and dual responders (164). The inflammatory progenitors and dendritic cells then can populate the bronchial airways and nasal mucosa (165).

Allergic asthma often occurs from ages 2 to 4 to 60+ years and has been recognized in the geriatric population (166,167). The use of the term *allergic asthma* implies that a temporal relationship exists between respiratory symptoms (clinical reactivity) and allergen exposure and that antiallergen IgE antibodies can be demonstrated or suspected. Approximately 75% to 90% of patients with persistent asthma have clinical reactivity or at least allergic sensitization depending on the study.

Respiratory symptoms may develop within minutes or in an hour after allergen exposure; however, they may not be obvious when there is uninterrupted allergen exposure. Common allergens associated with IgE-mediated asthma include pollens, such as from trees, grasses, and weeds; fungal spores; dust mites; animal dander; and in some settings, animal urine or cockroach excreta. IgE-mediated occupational asthma is considered under the category of occupational asthma. Allergen particle size must be less than 10 μm to penetrate into deeper parts of the lung because larger particles, such as ragweed pollen (19 μm), impact in the oropharynx. However, submicronic, "subpollen" ragweed particles have been described that could reach smaller airways (168). Particles smaller than 1 μm, however, may not be retained in the airways. Fungal spores, such as *Aspergillus* species, are 2 to 3 μm in size, and the major cat allergen (*Fel d 1*) has allergenic activity from 0.4 to >9 μm in size (169). Cat allergen is found in cat saliva, from sebaceous glands, and from skin. *Fel d 1* can be present in indoor air, on clothes, and in schoolrooms or in homes where no cats are present (169).

The potential severity of allergic asthma should not be minimized because experimentally, after an antigen-induced early bronchial response, bronchial hyperresponsiveness to an agonist such as methacholine or histamine can be demonstrated. This hyperresponsiveness precedes a late (3- to 11-hour) response (170). In addition, fungus-related (mold-related) asthma may result in a need for

intensive antiasthma pharmacotherapy, including ICS and even alternate-day prednisone in some patients. Exposure to *Aspergillus alternata,* a major fungal aeroallergen, was considered an important risk factor for respiratory arrests in 11 patients with asthma (171). The risk of asthma deaths is higher on days with mold spore counts >1,000/mm^3 (172). Dust mites and animal danders are important triggers of allergic asthma. Mouse urine and cockroach allergens (feces, saliva, and shedding body parts) are other indoor allergens that can be associated with allergic sensitization and severe asthma (173,174).

The diagnosis of allergic asthma should be suspected when symptoms and signs of asthma correlate closely with local patterns of pollinosis and fungal spore recoveries. For example, in the Upper Midwestern United States after a hard freeze in late November, which reduces (but does not eliminate entirely) fungal spore recoveries from outdoor air, patients suffering from mold-related asthma note a reduction in symptoms and medication requirements. When perennial symptoms of asthma are present, potential causes of asthma include animal dander, dust mites, cockroach excreta, mouse urine, and, depending on the local conditions, fungal spores and pollens. Cockroach allergen (*Bla g 1*) is an important cause of asthma in infested buildings, usually in low-socioeconomic areas. High indoor concentrations of mouse urine protein (*Mus d 1*) have been identified with volumetric sampling, and monoclonal antibodies directed at specific proteins suggested additional indoor allergens. The physician should correlate symptoms with allergen exposures, support the diagnosis by demonstration of antiallergen IgE antibodies, and institute measures when applicable to decrease allergen exposure (50). Patients with allergic asthma likely have allergic rhinitis, and uncontrolled allergic rhinitis is associated with less well-controlled asthma (175). It is advised to treat the upper and lower airways (176).

Some recommendations for environmental control have been made (1–4,50). There is evidence supporting a multicomponent home-based environmental control program (13). In a study of inner-city children with asthma, where 94% of children had at least one positive skin test to an indoor allergen, the interventions included home visits for teaching; creating a plan of action; allergen-impermeable encasings for the mattress, box spring, and pillows; and a high-efficiency particulate air (HEPA) filtered vacuum cleaner (13). If there were mold or animal sensitization or passive smoking, an HEPA air filter was used. For cockroach exposure and sensitization, professional pest control services were obtained. Twenty percent reduction in symptoms and days of wheeze with intensive environmental control measures was found to be as great

as what has been reported in studies of ICS (13). The beneficial effects of environmental control help support the notion of allergic asthma being exacerbated by indoor allergens.

Detection of a major cat allergen, *Fel d 1*, in homes or schools never known to have cat exposure is consistent with transport of *Fel d 1* into such premises and sensitivity of immunoassays for cat allergen. The removal of an animal from a home and effectively encasing a mattress and pillow are interventions known to decrease the concentration of allergens below which many patients do not have clinical asthma symptoms. Once a cat is removed from the home and cleaning occurs, it has been reported that it takes 20 to 24 weeks for the concentration of cat allergen to decrease to that found in homes without cats (177). A few homes had persistently high concentrations of *Fel d 1* over this period, and sources of residual cat dander were identified subsequently in those houses (177).

Although food ingestion can result in anaphylaxis, persistent asthma is not explained by IgE-mediated reactions to ingested food. Food production exposure, such as occurs in bakers (178), egg handlers, flavoring producers, and workers exposed to vegetable gums, dried fruits, teas (179), or enzymes (180), is known to produce occupational asthma mediated by IgE antibodies.

Nonallergic Asthma

In nonallergic asthma, IgE-mediated airway reactions to common allergens are not present. Nonallergic asthma occurs at any age range, as does allergic asthma, but the former is generally more likely to occur in subjects younger than 4 years of age or older than 60 years of age. Episodes of nonallergic asthma are triggered by ongoing inflammation or by upper respiratory tract infections, odors or air pollution, purulent rhinosinusitis, or exacerbations of chronic rhinosinusitis (CRS). Most patients have no evidence of IgE antibodies to common allergens. In youngsters, "transient early wheezers" have about a 70% likelihood of not having asthma by ages 9 to 11 years (160,181).

In other patients, skin tests or *in vitro* allergen tests are positive, but despite the presence of IgE antibodies, there is no temporal relationship between exposure and symptoms. Often, but not exclusively, the onset of asthma occurs in the setting of a viral upper respiratory tract infection. Virus infections have been associated with mediator release and bronchial epithelial shedding, which can lead to ongoing inflammation and asthma symptoms. Commonly recovered viruses that are associated with worsening asthma include picornaviruses

(rhinoviruses), coronaviruses, RSV, parainfluenza viruses, influenza viruses, and adenovirus. CRS can be identified in some patients with asthma, as can nasal polyps with or without aspirin intolerance (aspirin-exacerbated respiratory disease). Indoor air pollution (3,4) from volatile organic compounds, formaldehyde, wood burning stoves, and cigarette smoking can contribute to asthma of any kind including nonallergic asthma. It is important to consider occupation or hobby-related exposures that may in fact be IgE-mediated in patients with nonallergic asthma.

The T_H2 ("hygiene hypothesis") theory of asthma was supported in part by a study finding that protection against developing asthma in children aged 6 to 13 years was associated with day care attendance during the first 6 months of life or with having two or more older siblings at home (182). The "protected" children by age 13 years had a 5% incidence of asthma, compared with 10% in children who had not attended day care or who had one or no sibling (182). Of note is that at 2 years of age, the ultimately protected children had a 24% prevalence of wheezing, compared with 17% in nonprotected children. Overall, the frequent exposure to other children in early childhood, which is likely associated with more viral infections, could result in a T_H1 predominance as opposed to a T_H2 or allergy profile of CD4$^+$ lymphocytes.

Allergen immunotherapy is not indicated and will not be beneficial in patients with nonallergic asthma despite any presence of antiallergen IgE antibodies.

Potentially (Near) Fatal Asthma

The term *potentially (near) fatal asthma* describes the patient who is at high risk for an fatality from asthma (152,154). The initial series of patients with potentially fatal asthma had one or more of the following criteria: (a) respiratory acidosis or failure from asthma, (b) endotracheal intubation from asthma, (c) two or more episodes of acute severe asthma despite use of oral corticosteroids and other antiasthma medications, or (d) two or more episodes of pneumomediastinum or pneumothorax from asthma. Other factors have been associated with a potentially fatal outcome from asthma, and these criteria may not identify all high-risk patients (2,3). The NAEPP summary lists some additional factors associated with exacerbations or deaths including persistent severe airflow obstruction, acute severe airflow obstruction, and being frightened by one's asthma (3). The physician managing the high-risk patient should be aware of the potential of a fatality and strive to prevent this outcome (152,154). The impossible-to-manage patient who has both severe asthma and

nonadherence is referred to as having malignant, potentially fatal asthma (154).

Aspirin-Exacerbated Respiratory Disease (Aspirin-Induced Asthma)

Selected patients with asthma, often nonallergic, have acute bronchoconstrictive responses to aspirin and/or nonselective NSAIDs that inhibit cyclooxygenase-1 (23–26,183–189). The onset of acute bronchoconstrictive symptoms after ingestion of such agents can be within minutes (such as after chewing Aspergum) to within 3 hours (187,189). Some physicians accept a respiratory response that occurs within 8 to 12 hours after aspirin or NSAID ingestion; however, a shorter time interval seems more appropriate, such as up to 3 hours. In persistent asthma, variations in expiratory flow rates occur frequently, so that confirming that aspirin produces a reaction at 8 hours requires careful evaluation. The most severe reactions occur within minutes to 2 hours after ingestion. With indomethacin, 1 or 5 mg oral challenges have resulted in acute responses as have aspirin tablets being placed on the tongue to treat sore throat. Cross-reaction exists, such that certain nonselective NSAIDs that inhibit cyclooxygenase-1 (ibuprofen, indomethacin, flufenamic acid, and mefenamic acid) have a higher likelihood of inducing bronchospastic responses in aspirin-sensitive subjects than other NSAIDs. Because fatalities have occurred in aspirin sensitive subjects with asthma, challenges should be carried out only with appropriate explanation to the patient, with obvious need for the challenge (such as presence of rheumatoid arthritis or coronary artery disease), and by experienced physicians. Often, aspirin-sensitive patients can be desensitized to aspirin after experiencing early bronchospastic responses (183,185,187). Subsequent regular administration of aspirin does not cause acute bronchospastic responses.

From the historic perspective, the term *aspirin-exacerbated respiratory disease* (187,188) has replaced the term *aspirin triad or Samter triad* (189) and refers to aspirin-intolerant patients with asthma who have also chronic nasal polyps and CRS. The onset of asthma often precedes the recognition of aspirin intolerance by years. Approximately one-third to two-thirds of patients have immediate skin reactivity to common allergens. At one time, tartrazine (FD&C Yellow No. 5) was reported to result in immediate bronchospastic reactions in 5% of patients with the aspirin triad. Contrary results in double-blind studies have been reported in that none of the patients responded to the challenge or subsequent avoidance or tartrazine (190).

The drugs that produce such immediate respiratory responses share the ability

to inhibit the enzyme cyclooxygenase-1, which is known to metabolize arachidonic acid into PGD_2, $PGF_{2\alpha}$, and thromboxanes. Structurally, these drugs are different, but they have a common pharmacologic effect. Data suggest that the blockade of cyclooxygenase-1 diverts arachidonic acid away from production of PGE_2, with loss of its "braking effects" on the lipoxygenase pathway. This effect results in unrestrained overproduction of LTC_4 and LTD_4 (23–26,186,187). The latter is a potent bronchoconstrictive agonist. Patients with aspirin-exacerbated respiratory disease have higher baseline $PGF_{2\alpha}$ concentrations and higher urinary LTE_4 concentrations (25) than aspirin-tolerant patients with asthma. After aspirin ingestion, intolerant patients have profound increases in urinary LTE_4 compared with aspirin-tolerant subjects (25). When bronchial biopsy specimens were obtained from aspirin-intolerant and aspirin-tolerant patients with asthma, there were many more cells (primarily activated eosinophils, but also mast cells and macrophages) that expressed LTC_4 synthase in the aspirin-intolerant patients (26). This critical finding supports the urinary LTE_4 results, which are the marker for the bronchoconstrictor LTD_4 that requires LTC_4 synthase for generation. In other words, these data support a "knock-in" as opposed to a "knock-out" state. It has been demonstrated that after aspirin or nonselective NSAID ingestion, there is a decline in the protective PGE_2, whose main effect is the "brake" on synthesis of 5-lipoxygenase (5-LO) and 5-lipoxygenase-activating protein (FLAP) (187). The lack of or reduced inhibition of these two key enzymes in the lipoxygenase pathway, allows for excessive generation of LTC_4 at baseline and after aspirin or nonselective NSAID ingestion. The overexpression of LTC_4 synthase primarily by eosinophils results in profound increases in LTD_4 after aspirin or a nonselective cyclooxygenase inhibitor is ingested. Bronchial biopsies have not identified differential staining for cycloxygenase-1, cyclooxygenase-2, 5-LO, LTA_4 hydrolase, or FLAP in aspirin-intolerant versus aspirin-tolerant patients (191). The effects of excessive LTD_4 production appear to be amplified by increased numbers of its receptor, specifically cysteinyl leukotriene type 1 receptor as compared to cysteinyl leukotriene type 2 receptor (192,193). In addition, there are four receptors for prostaglandin E (E-prostanoids 1-4 designated as EP), yet EP2 is reduced in bronchial and nasal mucosa in patients with aspirin-exacerbated respiratory disease (194). EP-2 stimulation results in production of cyclic adenosine monophosphate (AMP), which leads to bronchodilation. This protective response is reduced in aspirin-exacerbated respiratory disease (194).

Mast cell activation occurs after aspirin challenges as well. There are increases in histamine (and LTC_4) in bronchial lavage and nasal fluid after aspirin challenges (195). In some patients, there is an increase in tryptase and PGD_2, a potent bronchoconstrictor, vasodilator, and chemoattractant for eosinophils (196). From the practical perspective, in virtually all patients, selective cyclooxygenase-2 inhibitors will be tolerated safely in aspirin-intolerant patients (186,187).

Occupational Asthma

Occupational asthma has been estimated to occur in 5% to 10% of all patients with asthma (100). Specific industry prevalence of occupational asthma may be even higher (e.g., 15.8% in snow crab processors in Canada) (197). Occupational asthma may or may not be IgE mediated. When it is IgE mediated, longitudinal data support a time of sensitization, followed by development of bronchial hyperresponsiveness and then bronchoconstriction (197). After removal from the workplace exposure, the reverse sequence has been recorded. At the time of removal from exposure, factors associated with persistent asthma include having symptoms for more than 1 year, having abnormal pulmonary function tests, and taking asthma medications. Malo et al. (198) documented that spirometry and bronchial hyperresponsiveness in patients no longer working with snow crabs reached a plateau of improvement by 2 years after cessation of work exposure. In workers with occupational asthma attributable to detergent enzymes such as proteases, amylase, and cellulases, many of the workers continued to report respiratory symptoms 3 years after removal from the workplace (see Chapter 25). Occupational asthma has been recognized among health care professionals (from 4.2% in physicians to 7.3% in nurses) (100,199). It is appreciated that some of the cases are irritant as opposed to allergic. The assessment of patients with possible occupational asthma is discussed in detail in Chapter 25. Some workers have early, late, dual, or irritant bronchial responses, such as occur to trimellitic anhydride, which is used in the plastics industry as a curing agent in the manufacture of epoxy resins.

The differential diagnosis of occupational asthma is complex and includes consideration of irritants, smoke, toxic gases, metal exposures, insecticides, organic chemicals and dusts, infectious agents, and occupational chemicals. In addition, one must differentiate true occupational asthma from exposed workers who have coincidental adult-onset asthma not affected by workplace exposure. Some workers have chemical exposure and a compensation syndrome, but no objective asthma despite symptoms and usually a poor response to medications.

One must exclude work-related neuroses with fixation on an employer as well as a syndrome of reactive airways dysfunction, which occurs after an accidental exposure to a chemical irritant or toxic gas (200). Atopic status and smoking do not predict workers who will become ill to lower molecular-weight chemicals. Atopic status and smoking are predictors of IgE-mediated occupational asthma to high-molecular-weight chemicals. For example, Western red cedar workers display bronchial hyperresponsiveness during times of exposure, with reductions in hyperresponsiveness during exposure-free periods.

The complexity of diagnosing occupational asthma cannot be underestimated in some workers. Respiratory symptoms may intensify when a worker returns from a vacation but may not be dramatic when deterioration occurs during successive days at work. In patients with preexisting asthma, fumes at work may cause an aggravation of asthma without having been the cause of asthma initially.

Avoidance measures and temporary pharmacologic therapy can suffice to help confirm a diagnosis in some cases. Resumption of exposure should produce objective bronchial obstruction and clinical changes. The physician must be aware that workers may return serial PEFR measurements that coincide with expected abnormal values during work or shortly thereafter. Such values should be assessed critically because they are effort dependent and may be manipulated. Demonstration of IgE or IgG antibodies to the incriminated workplace allergen or to an occupational chemical bound to a carrier protein has been of value in supporting the diagnosis of occupational asthma from trimellitic anhidride and even in prospective use to identify workers who are at risk for occupational asthma (201). Such assays are not commonly available but are of discriminatory value when properly performed.

If a bronchial provocation challenge is deemed necessary, it is preferable to have the employee perform a job-related task that exposes him or her to the usual concentration of occupational chemicals. Subsequent blinding may be necessary as well, and successive challenges may be needed. The PC_{20} to histamine can decrease after an uneventful challenge, but the next day, when the employee is exposed to the incriminated agent again, a 30% decline in FEV_1 can occur, which confirms the diagnosis.

Exercise-Induced Asthma/Bronchoconstriction

Exercise-induced asthma occurs in response to either an isolated disorder in patients with intermittent asthma or an inability to complete an exercise program

in symptomatic patients with persistent asthma. Control of the latter often permits successful participation in a reasonable degree of exercise. In patients with intermittent asthma, whose only symptoms might be triggered by exercise, the pattern of bronchoconstriction is as follows: during initial exercise, the FEV_1 is slightly increased (about 5%), unchanged, or slightly reduced, but no symptoms occur. This is followed by declines of FEV_1 and onset of symptoms 5 to 15 minutes after cessation of exercise. The decline of FEV_1 is at least 10% (202,203). Airway hyperresponsiveness is present in the patients with asthma, and there is an increase in eNO (204). The term *exercise-induced bronchoconstriction* (EIB) refers to airway closure that occurs only with exercise, especially common in elite athletes. Not all of these athletes have hyperresponsive bronchi when challenged with histamine or methacholine as direct agonists; some athletes react only to indirect agonists, such as mannitol and hypertonic saline (4.5%) This finding has led to the notion that there may be injury to the airway in elite athletes as opposed to airway inflammation that characterizes asthma.

Exercise-induced asthma resulting in a decline in FEV_1 of at least 10% is associated with inspiration of cold or dry air. In general, greater declines in spirometry and the presence of respiratory symptoms are directly proportional to the level of hyperventilation and inversely proportional to inspired air temperature and humidity. The mechanism of bronchoconstriction is considered to be related to an increase in osmolarity of the periciliary fluid that accompanies the necessary conditioning of inspired air (202,205). It has been considered that the loss of water is able to increase the osmolarity of the periciliary fluid to over 900 mOsm so that there is bronchoconstriction (205). Another explanation is that postexertional airway rewarming causes increased bronchial mucosal blood flow as a possible mechanistic explanation (206). The evidence for rewarming has been difficult to prove, however. Clinically, it has been recognized that running outdoors while inhaling dry, cold air is a far greater stimulus to asthma than swimming or running indoors while breathing warmer humidified air. It has been argued that the hyperventilation of exercise causes a loss of heat from the airway, which is followed by cooling of the bronchial mucosa. In addition, there are greater declines in FEV_1 during exercise when there are higher levels of eosinophils in induced sputum. This finding supports an association between eosinophilic inflammation and exercise-induced asthma.

EIB can occur in any form of asthma on a persistent basis but can also be prevented completely or to a great extent by pharmacologic treatment. In

prevention of isolated episodes of EIB, medications such as short-acting inhaled β-adrenergic agonists inspired 10 to 15 minutes before exercise often prevent significant exercise-associated symptoms. Long-acting β_2-adrenergic agonists are also bronchoprotective but not recommended as stand-alone pretreatment. Cromolyn by inhalation is effective, as to a lesser extent are short-acting muscarinic antagonists and theophylline. Leukotriene receptor antagonists have a positive but more modest protective effect and suggest that LTD_4 participates in EIB. Histamine$_1$ antihistamines may provide bronchoprotection in some subjects. For patients with persistent asthma, overall improvement in respiratory status by avoidance measures and regular pharmacotherapy can minimize exercise symptoms. Pretreatment with short- or long-acting β_2-adrenergic agonists in addition to scheduled antiasthma therapy can allow asthma patients to participate in exercise activities successfully. ICS can help modify the extent of decline in FEV_1 from exercise.

The differential diagnosis of EIB includes unexpected dynamic collapse of the bronchi during strenuous exercise. The diagnosis is confirmed by CT examination of the bronchi showing excessive narrowing and with bronchoscopy (207).

Variant Asthma

Most patients with asthma report symptoms of coughing, chest tightness, and dyspnea, and the physician can auscultate wheezing or rhonchi on examination. *Variant asthma* refers to asthma with the primary symptoms of paroxysmal and repetitive coughing or dyspnea in the absence of wheezing (6). The coughing often occurs after an upper respiratory infection, exercise, or exposure to odors, fresh paint, or allergens. Sputum is usually not produced, and the cough occurs on a nocturnal basis. Antitussives, expectorants, antibiotics, and use of intranasal corticosteroids do not suppress the coughing. The chest examination is free of wheezing or rhonchi. McFadden (208) documented increases in large airways resistance, moderate-to-severe reductions in FEV_1 (mean, 53%), and bronchodilator responses. The mean RV was 152%, consistent with air trapping. In addition, patients with exertional dyspnea as the prime manifestation of asthma had an FEV_1 value still within normal limits but an RV of 236% (208) and not greatly increased airways resistance. Both phenotypes had reduced small airways flow rates. Some patients can be induced to wheeze after exercise or after performing an FVC maneuver.

Pharmacologic therapy can be successful to suppress the coughing episodes

or sensation of dyspnea. When inhaled, β_2-adrenergic agonists have not been effective; the best way to suppress symptoms is with an orally ICS. If using an inhaler produces coughing, a 5- to 7-day course of oral corticosteroids often stops the coughing (6,7). At times, even longer courses of oral corticosteroids and antiasthma therapy are necessary.

Factitious Asthma

Factitious asthma presents diagnostic and management problems that often require multidisciplinary approaches to treatment (159,209). The diagnosis may not be suspected initially because patient history, antecedent triggering symptoms, examination, and even abnormal pulmonary physiologic parameters may appear consistent with asthma. Nevertheless, there may be no response to appropriate treatment or, in fact, worsening of asthma despite what would be considered effective care. Some patients are able to adduct their vocal cords during inspiration and on expiration, emit a rhonchorous sound, simulating asthma. Other patients have repetitive coughing paroxysms or "seal barking" coughing fits. A number of patients with factitious asthma are physicians, nurses, or paramedical personnel who have an unusual degree of medical knowledge. Psychiatric disease can be severe, yet patients seem appropriate in a given interview. Factitious asthma episodes do not occur during sleep, and the experienced physician can distract the patient with factitious asthma and temporarily cause an absence of wheezing or coughing. Invasive procedures may be associated with conversion reactions or even respiratory "arrests" from breath-holding.

Vocal Cord Dysfunction and Asthma

VCD (also called *laryngeal dyskinesia*) may coexist with asthma (143,144,210–212) (Fig. 19.4B). In a series of 95 patients with VCD, 53 patients had asthma. The level of medication prescriptions can be very high in patients with VCD with or without asthma (143). Of great concern is the prolonged use of oral corticosteroids for dyspnea that is, in fact, due to VCD and not from asthma. Patients with VCD and asthma may or may not have insight into the VCD. Some patients can be taught by a speech therapist to avoid vocal cord adduction during inspiration. In particular, they can learn abdominal in place of thoracic breathing on inspiration. The diagnosis can be suspected when there is a truncated inspiratory loop on a flow-volume loop, when direct visualization of the larynx identifies vocal cord adduction on inspiration, on CT examination of the neck (143,144, 210–212), or by bedside examination. In the latter case, the

patient may have a diagnosis of asthma and be hospitalized. Although symptoms are present, the patient has limited wheezing or a quiet chest, relatively normal blood gases or pulse oximetry, and is unwilling to phonate the vowel "e" for more than 3 seconds. In addition, when prompted, there is no large inspiratory effort made. In the series of 95 patients, many were health care providers and females who were obese (143). GERD was present in 15 of 40 (37.5%) patients who had both VCD and asthma, compared with 11 of 33 (33%) with VCD without asthma (143). In all, 95 patients (38%) had a history of abuse, such as physical, sexual, or emotional (143). VCD should be suspected in difficult-to-control patients with severe (typically corticosteroid-dependent asthma) in patients whose symptoms or medical requirements do not concur with the relatively normal spirometric or arterial blood gas findings, and in those who have prolonged hoarseness with dyspnea, wheezing, or coughing, with or without asthma.

Coexistent Asthma and Chronic Obstructive Pulmonary Disease

Usually, in the setting of long-term cigarette smoking (at least 30 to 40 pack-years), asthma may coexist with COPD. Obviously, the patients with asthma or COPD should not smoke. Multiple medications may be administered in patients with asthma and COPD to minimize signs and symptoms. However, some dyspnea likely will be fixed and not transient because of the underlying COPD. The component of asthma can be significant, perhaps 25% to 50% initially. However, with continued smoking, the reversible component, using oral and ICS, β_2-adrenergic agonists, combined ICS/long-acting β_2-adrenergic agonist, theophylline, tiotropium, and leukotriene antagonists, diminishes or becomes nonexistent. At that point, the fewest medications possible should be used. When there is no benefit from oral corticosteroids, it is advisable to taper and discontinue them.

Initially, such as after hospitalization for asthma, the patient with combined asthma and COPD may benefit from a 2- to 4-week course of oral corticosteroids. The effort to identify the maximal degree of reversibility should be made even when asthma is a modest component of COPD. The lack of bronchodilator responsiveness or peripheral blood eosinophilia does not preclude a response to a 2-week course of prednisone.

Long-term care of patients with coexistent asthma and COPD can be successful in improving quality of life and reducing or eliminating disabling

wheezing. A combination of ICS and long-acting β_2-adrenergic agonist can improve patient outcomes (213,214). However, eventually, patients may succumb to end-stage COPD or coexisting cardiac failure.

The asthma–COPD overlap syndrome refers to patients whose response to albuterol is quite large (for $FEV_1 \geq 15\%$ and ≥ 400 mL) despite evidence of airways obstruction ($FEV_1/FVC < 0.70$) (12). However, there remains controversy over which criteria are the most useful for the diagnosis (215).

■ NONANTIGENIC PRECIPITATING STIMULI

Hyperresponsiveness of bronchi in patients with asthma is manifested clinically by responses to various nonantigenic triggers. Some airborne triggers include odors, such as cigarette smoke, fresh paint, cooking odors, perfumes, cologne, insecticides, and household cleaning agents (216). In addition, sulfur dioxide, ozone, nitrogen dioxide, carbon monoxide, and other combustion products, both indoors and outdoors, can trigger asthma signs and symptoms. Emergency department visits for asthma in adults in New York City peaked 2 days after increases in ambient air ozone levels (217). The effect was most pronounced in patients who had smoked more than 14 pack-years of cigarettes (217). There was no ozone effect for adult nonsmokers or light smokers (<13 pack-years) with asthma. In this study, most patients had persistent severe asthma, and there was no effect of relative humidity on emergency department visits. These data support an effect of ozone on patients with severe asthma who were cigarette smokers. Adverse effects of ozone were not found in light or nonsmokers. It is clear that air pollution from oxidant gases (ozone, nitrogen dioxide, and sulfur dioxide) is associated with emergency department visits for asthma and wheezing (218). Bronchoconstriction likely occurs on an irritant basis. Effective management of patients with asthma may permit patients to tolerate most inadvertent exposures with little troubling effects. Diesel exhaust particles have been shown to stimulate increases in allergen-specific IgE antibodies and increase IL-4 and IL-13 production. Further, these particles were able to induce isotype switching from IgM to IgE antibodies in B cells (219). The public health effects of diesel exhaust particles may be very great both on emergence of allergen responses (219) when considered combined with the findings that children living closer to high traffic highways had more emergency visits for asthma (220,221).

GERD has been a recognized trigger of asthma episodes (3,4,222–224). Frank GERD with aspiration into the bronchi has been associated with chronic cough,

episodic wheezing, rhonchi, and even cyanosis if aspiration is severe. Reflux of gastric acid into the lower esophagus can precipitate symptoms of asthma or cough without frank aspiration, perhaps by microaspiration or an esophagobronchial vagal reflex. While patients with asthma and GERD who have undergone esophageal acid infusion have demonstrated increases in airways resistance and decreases in PEFR, patients with asthma without GERD can also have these changes. An acute episode of asthma or COPD can cause increased negative intrathoracic pressures, which can increase reflux. The comorbidities of asthma and GERD remain very pertinent in that there is evidence of GERD using pH probes in 30% to 65% of US veterans (222).

Medical therapy for GERD, such as avoiding meals for 3 hours before recumbency, weight reduction, cessation of cigarette smoking, discontinuation of drugs that decrease gastroesophageal sphincter tone (theophylline), diet manipulation, and raising the head of the bed 6 inches and sleeping in the left lateral decubitus position, may be of value. There is expert consensus opinion that elevation of the head of the bed and sleeping in the left lateral decubitus position can help reduce the symptoms of reflux (223). Pharmacotherapy with protein-pump inhibitors (PPIs) for 3 months is advisable and then an assessment should be made regarding continued therapy. Some patients will benefit from twice-daily PPI (taken 30 minutes before breakfast and dinner) and a histamine$_2$ receptor antagonist at bedtime. Surgical intervention is indicated occasionally for patients who fail medical therapy (3 months). Approaches that have been successful in varying degrees are with either laparoscopic fundoplication or open procedures in patients with large hiatal hernias, strictures, or previous surgery. Nonacid or weakly acidic reflux also contributes to cough and may be present when there has been an inadequate response to twice-daily, PPI therapy with or without a histamine$_2$-receptor antagonist (224). Nevertheless, it should be appreciated that empiric PPI therapy in the absence of reflux, administered for insufficiently controlled asthma, has not been found efficacious (225).

Some patients with asthma have "atypical reflux" which is considered a preferable description for supraesophageal reflux disease (SERD) or laryngopharyngeal reflux (LPR), characterized by hoarseness, throat clearing, globus sensation, and persistent cough. Other patients have nonerosive reflux disease (NERD), in which case the endoscopic exam reveals little or no evidence of reflux and there are normal esophageal pH measurements despite symptoms consistent with GERD.

CRS (see Chapter 27) and acute exacerbations of rhinosinusitis can cause

acute severe asthma or exacerbations of asthma. Patients with intermittent asthma may experience an exacerbation of asthma in the setting of acute rhinosinusitis, upper respiratory tract infection, or community-acquired pneumonia. Common variable immunodeficiency or specific antibody deficiency (see Chapter 4) may be diagnosed in the patient with an infectious cause for an exacerbation of asthma or CRS and persistent asthma.

Left-sided CHF has been associated with exacerbations of asthma. Bronchial hyperresponsiveness has been recognized in nonasthmatic patients who developed left ventricular failure. When patients with asthma develop CHF, at times, sudden episodes of wheezing dyspnea can occur in the absence of neck vein distention or peripheral edema, which would support a diagnosis of left ventricular failure. Differentiating pulmonary edema from acute asthma may be difficult in brittle cardiac patients who have persistent moderate or severe asthma or asthma, COPD, and left ventricular failure. B-type natriuretic peptide or troponin can be elevated in the setting of left ventricular failure (226). Transthoracic echocardiography, in the emergency setting, can demonstrate evidence of CHF (226). Acute pulmonary emboli may present as exacerbations of asthma, acute dsypnea in a patient with asthma, or an exacerbation of CHF in a patient with persistent asthma.

DIFFERENTIAL DIAGNOSIS OF WHEEZE, DYSPNEA, AND COUGH

There are many causes of wheezing, dyspnea, and coughing, individually and collectively. A partial listing is as follows:

I. Commonly encountered diseases or conditions

  A. Asthma

  B. Upper respiratory tract infection

     1. Bronchiolitis

     2. Croup

     3. Viruses (e.g., RSV, rhinovirus, influenza, parainfluenza, metapneumovirus, etc.)

     4. Acute and chronic bronchitis

     5. Acute nonhospital (community)-acquired pneumonia

     6. Bronchiectasis

7. Rhinosinusitis

C. CHF

    1. Left ventricular failure

    2. Mitral stenosis

    3. Congenital heart disease

D. COPD

E. Hyperventilation syndrome

F. Pulmonary infarction or embolism

G. Cystic fibrosis

H. VCD

I. Laryngotracheomalacia

J. Bronchopulmonary dysplasia

K. Vascular rings

L. GERD

II. Less common conditions

A. Tuberculosis

B. Hypersensitivity pneumonitis (avian or microorganisms, e.g., fungi and bacteria)

C. Inhalation of irritant gases, odors, or dusts

D. Physical obstruction of the upper airways

    1. Neoplasms (benign or malignant)

    2. Foreign bodies

    3. Acute laryngeal or pharyngeal angioedema

    4. Bronchial stenosis

        a. Postintubation

        b. Granulomatous

        c. Postburn

E. Interstitial lung disease

    F. *Pneumocystis carinii* pneumonia

    G. Sarcoidosis

    H. Bronchomalacia

III. Uncommon conditions

    A. Restrictive lung disease

    B. EGPA (Churg–Strauss syndrome)

    C. Mediastinal enlargement

    D. Diphtheria

    E. Carcinoid tumor of main-stem bronchi

    F. Thymoma

    G. Tracheoesophageal fistula

    H. ABPA

    I. α_1-Antitrypsin deficiency

    J. Factitious coughing, wheezing, or stridor

    K. Dynamic airway collapse

TREATMENT

As in other chronic illnesses, the basic objectives of asthma treatment are to significantly control symptoms and prevent physical and psychologic impairment (3,4). This most often is achieved through a combination of pharmacologic and nonpharmacologic strategies directed in part by the acuity, severity, and classification of the underlying disease (Tables 19.5 to 19.7). The ultimate objective in managing asthma is for patients to be able to lead normal, functional lives with little or no impairment in exercise or sleep. Additionally, lung function should be preserved to avoid excessive losses in FEV_1. The practical goals of asthma treatment are best measured by avoidance of fatalities, hospitalizations, and school or work absenteeism/presenteeism. When selecting a particular asthma therapy, it is important to consider factors that will impact patient adherence, including side effect profiles and cost. Finally, individualized treatment plans should be created because patients can have variable clinical responses to the same therapeutic. The NAEPP Expert Panel Report 3 suggests considering three dimensions: the level of severity, control, and responsiveness (ease of treatment) (3).

TABLE 19.7 GOALS OF THERAPY IN MANAGEMENT OF ASTHMA
Prevent fatalities
Maximize asthma control
Prevent hospitalizations, emergency department visits and unscheduled care visits
Prevent/reduce nocturnal asthma
Prevent/reduce limitations of activities, school/work absenteeism/presenteeism
Maximize respiratory status and pulmonary function. Use appropriate medications
Prepare an action plan for exacerbations (know the patient)

Principles

Asthma is a complex disease. The approach to asthma treatment is multifactorial and consists of determining the clinical classification (Table 19.5), the functional classification (Table 19.6), necessary avoidance measures, pharmacologic therapy, and, when indicated, allergen immunotherapy and immunobiologic treatments (Tables 19.7 to 19.9). When asthma symptoms persist despite extensive medical therapy, alternative medical diagnoses and conditions should also be considered.

The pharmacologic treatment of asthma consists of therapeutic measures to reduce inflammation and to reverse bronchial mucosal edema, bronchospasm, hypersecretion of mucus, and V/Q imbalance. This is achieved by targeting a variety of cellular and molecular mechanisms important in asthma pathogenesis, including smooth muscle contraction, tissue remodeling, leukocyte recruitment, and inflammatory mediator release. There are currently seven major classes of medications used to manage asthma from acute exacerbations to chronic symptoms. Some of these therapeutics have been used for over half a century, whereas other agents were approved only within the year. Additionally, numerous novel agents are currently being designed or are in clinical trials.

Drug Therapy

Corticosteroids

Glucocorticoids are a class of steroid hormones naturally produced in the adrenal cortex and important in regulating inflammation, glucose metabolism, and many other critical physiologic processes (see Chapter 35). Synthetic corticosteroids are the most effective drug in the treatment of asthma and are available in oral, subcutaneous, intravenous, and topical formulations. Glucocorticoids act by binding to their cytoplasmic receptor, the glucocorticoid receptor. Once bound, the hormone–receptor complex then translocates into the cell nucleus to induce a variety of anti-inflammatory responses through (1) upregulation of various anti-inflammatory genes, (2) downregulation of pro-inflammatory genes, (3) repression of the pro-inflammatory protein NF-κB, and (4) destabilization and reduction of various mRNA (see Table 19.11). From these mechanisms, glucocorticoids play a wide role in suppressing inflammation in part by reducing the number and activation of inflammatory cells (e.g., eosinophils, basophils, mast cells) as well as decreasing microvascular leak and smooth muscle tissue remodeling.

Parenteral Corticosteroids

Parenteral corticosteroids are often not only used in the treatment of acute asthma exacerbations but can also be used as treatment in severe persistent disease as discussed below. These agents include *Dexamethasone* (Decadron), *Hydrocortisone* (Cortef), *Methylprednisolone* (Solumedrol), *Prednisone*, and *Prednisolone* (Orapred). One of the major differences among these glucocorticoids is their relative potency. Dexamethasone is about 25 times more potent, methylprednisolone 5 times, and prednisone 4 times more potent than hydrocortisone. The clinical efficacy of one specific drug versus another in the treatment of asthma has not been directly evaluated by independent rigorous studies.

TABLE 19.8 ACUTE ASTHMA TIPS

IN THE EMERGENCY DEPARTMENT

1. Establish severity of asthma:

   Cannot speak in a sentence?

   Accessory muscle use?

   Cyanotic?

Heart rate 120 beats/minute or greater?

Cannot perform spirometry or peak flow is less than 200 L/minute?

β_2-adrenergic agonist overuse?

Marked nocturnal symptoms?

2. Send the patient who clears after emergency therapy home with a short course of oral corticosteroids. Arrange follow-up care.

1. Does the patient need hospitalization or emergency therapy?

2. A combination of regular β_2-adrenergic agonist and inhaled corticosteroid may suffice. Otherwise add a short course of an oral corticosteroid.

3. Check inhaler technique.

4. Schedule follow-up care.

5. Consider referral to an allergist-immunologist.

TABLE 19.9 PERSISTENT ASTHMA TIPS

1. Appreciate limitations of inhaled β_2-adrenergic agonists, inhaled corticosteroids, muscarinic antagonists, cromolyn, leukotriene receptor antagonists and biosynthesis inhibitors, and theophylline.

2. Check and improve inhaler technique even in patients using spacer devices.

3. Reassess the patient after initial therapy and change management if satisfactory improvement has not occurred.

4. Emphasize anti-inflammatory therapy as opposed to scheduled β_2-adrenergic agonists (and possibly theophylline).

5. Address allergic factors at home, school, and workplace. Consider referral to an allergist-immunologist.

6. Exclude ABPA.

7. Many patients are managed successfully with inhaled corticosteroids with or without β_2-adrenergic agonists.

8. Avoid excessively demanding medication regimens.

9. Arrange for emergencies or deteriorations in respiratory status by involving the patient or family, if possible.

10. Use oral corticosteroids early to decrease asthma symptoms in a patient who has

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11. Identify patients with potentially (near) fatal asthma.

12. Address co-morbidities or phenotypes (GERD, rhinosinusitis, allergic rhinitis, depression, anxiety, non-adherence, obstructive sleep apnea, specific antibody deficiency, common variable immunodeficiency etc).

ABPA, allergic bronchopulmonary aspergillosis; GERD, gastroesophageal reflux disease.

Inhaled Corticosteroids

ICS are the recommended treatment of choice for patients with persistent mild, moderate and severe asthma with the benefits of treatment confirmed by many investigations (3,4) (see Chapters 22 and 35 and Table 19.6). As with parenteral glucocorticoids, there are several inhaled glucocorticoids from which to choose: *Beclomethasone dipropionate* (Qvar), *Budesonide* (Pulmicort), *Ciclesonide* (Alvesco), *Flunisolide* (Aerobid, Aerospan), *Fluticasone propionate* (Flovent), *Flucticasone furoate* (Arnuity), *Mometasone* (Asmanex), and *Triamcinolone acetonide* (Azmacort). The recommended treatment dose is based upon the degree of asthma severity and varies among the different agents. While most of the ICS compounds are available in their active state, ciclesonide is a pro-drug that is hydrolyzed to its pharmacologically active metabolite, des-ciclesonide, in the nasal mucosa and lungs.

Another factor differentiating inhaled glucocorticoids is the type of delivery device. Budesonide and mometasone are available as dry-powder inhalers which are breath actuated. In contrast, beclomethasone dipropionate, ciclesonide, flunisolide, and triamcinolone acetonide are available as MDIs which are pressurized aerosols. Fluticasone is currently available in both formulations. The patient's ability to correctly use a particular device should be an important consideration when prescribing inhaled glucocorticoids.

Glucocorticoids and Management of Persistent Asthma

Chronic (scheduled) administration of ICS is associated with improved asthma control (227,228). Additionally, these agents can prevent work and school absenteeism, disabling wheezing, and episodes of acute severe asthma or respiratory failure in patients with persistent severe asthma. Although it is possible to utilize an ICS on an as-needed basis in patients who truly have persistent mild asthma (141), daily therapy is more routinely prescribed (228). In an early study of newly diagnosed patients with mild asthma, budesonide, 600 μg twice daily, was considered superior to inhaled β_2 agonist, terbutaline, 375 μg

twice daily (229). Patients were treated for 2 years with this moderately high dose of budesonide and then received budesonide, 400 µg/day or placebo (230). Not surprisingly, patients who received budesonide had better asthma control (FEV_1, peak flow, and bronchial responsiveness) than placebo-treated controls (230). However, in a separate large study, there was no dose–response relationship observed between ICS use and avoidance of hospitalizations from asthma (231). As such, effective dosages should be used, but with a flat dose–response effect, larger doses of ICS may produce little additional benefit with increased unwanted side effects.

As with other medications, there is significant variability of response with ICS. Some patients have >15% improvements in FEV_1, whereas others have poor responses (<5% improvement in FEV_1) (232). In a study of patients with mild asthma and in which bronchodilator reversibility was not used as an inclusion criterion, the response to ICS over 6 weeks was split into responders (54%) and nonresponders (46%) (87). In the best responders, the FEV_1 improved by as much as 60% and the authors suggested a good short-term response to ICS could predict long-term asthma control (87,233). Unfortunately, ICS administered to high-risk toddlers and young children have not been associated with prevention or suppression of the emergence of asthma (234–236).

Some patients with severe persistent asthma cannot be controlled effectively on ICS, and thus oral corticosteroids may be warranted. Oral corticosteroids may be associated with more significant side effects and their use should be used judiciously, keeping in mind that failure to utilize them when indicated may result in unwarranted morbidity and mortality. If corticosteroids are still required after 3 weeks of daily use for severe asthma, alternate-day prednisone therapy should be considered to minimize the occurrence of adverse side effects. The total daily dose of a short-acting corticosteroid (prednisone, prednisolone, and methylprednisolone) should be taken in the morning every 48 hours, as long as the underlying airways obstruction is controlled adequately, with split daily doses being avoided in stable ambulatory patients. On an alternate-day regimen, most patients obtain adequate control of symptoms with little, if any, deterioration in pulmonary function (237).

Glucocorticoids and Acute Asthma Exacerbations

In some adult patients whose asthma is controlled with 200 to 400 µg of budesonide or equivalent corticosteroid, doubling the dose may be adequate

during a mild exacerbation. More often, however, doubling the dose of ICS may not be beneficial when the patient is already receiving recommended doses (238). Quadrupling the ICS has been studied but didn't quite meet statistical significance (239). As such, in patients with persistent moderate-to-severe asthma, during exacerbations, oral corticosteroids are frequently indicated. Even patients with intermittent asthma or persistent mild asthma may require a short course of oral corticosteroids during an acute exacerbation.

Oral corticosteroids can prevent repeated emergency department or office visits in acutely ill patients who respond to β_2-adrenergic agonists and do not require hospitalization. A prednisone dosage regimen of 30 to 60 mg each morning for 5 to 7 days is often effective in adults, and in children 1 to 2 mg/kg prednisone is necessary, often the latter dosage for the first few days. For emergency department treatment, parenteral corticosteroids are typically prescribed with a minimum dosage of methylprednisolone 80 mg/day being as effective as higher dosages (240). Objective evidence of improvement in flow rates and FEV_1 in patients with acute severe asthma exacerbations requires about 12 hours of therapy (241). However, in some patients, beneficial effects can occur by 6 hours (242).

In the emergency department, the administration of systemic corticosteroids within the first hour of presentation has been shown to significantly reduce the number of hospitalizations (243). Additionally, short-term outpatient administration of corticosteroids decreases the incidence of return visits to emergency medical facilities (244,245). In a study in which all patients received 50 mg prednisone daily for the first 7 days after treatment in the emergency department for an asthma exacerbation, the use of high-dose budesonide (1,600 µg daily) resulted in an almost 50% reduction in relapses (12.8% vs. 24.5%) over a 21-day follow-up period (246). Thus, in addition to systemic corticosteroids, high and frequent doses of ICS appear to be beneficial in emergency department treatment of asthma exacerbations (247).

Corticosteroids are essential treatment in life-threatening asthma, but because of their delayed onset of action, they cannot replace other necessary emergency measures, including β_2-adrenergic agonists, patent airway, and oxygen. Patients who are still wheezing after initial emergency treatment with β_2-adrenergic agonists are in acute severe asthma (status asthmaticus) and should receive systemic corticosteroids. Patients who must be hospitalized for exacerbations of asthma should receive systemic corticosteroids immediately without attempting to determine whether continued β_2-adrenergic agonists (and possibly

ipratropium bromide or theophylline) would be sufficient.

For status asthmaticus, intravenous corticosteroids are usually administered. Hydrocortisone (400 mg/day), prednisone (100 mg/day), methylprednisolone (80 mg/day), and dexamethasone (12 mg/day) are the minimum effective dosages and are often as effective as higher dosages (240). Status asthmaticus can be managed with oral corticosteroids if access is difficult or if there are shortages of parenteral agents. The minimum equivalent dose for adults is prednisone 100 mg/day.

For malignant, potentially fatal asthma, intramuscular methylprednisolone can be a short-term consideration. It is available in 20-, 40-, and 80-mg/mL preparations for injection into the gluteus maximus. An alternative is triamcinolone acetonide at 10 mg/mL or 40 mg/mL For adults who can be considered nonadherent and unreliable, a dose of 40 to 120 mg can be given to try to prevent a hospitalization or potential fatality from asthma. Regular administration should be avoided unless there is no other alternative.

Glucocorticoids as a Diagnostic Tool

In addition to their therapeutic importance, corticosteroids may be useful as a diagnostic tool (6). Often, it is helpful to document the extent of reversibility of a patient's signs and symptoms to establish whether the basic underlying process is reversible as in asthma or instead irreversible obstructive airway disease. Therapeutic doses of corticosteroids for 7 to 14 days should significantly reverse the airway obstruction of asthma in almost all patients but would result in little or no reversal in most patients with chronic bronchitis or emphysema. The initial therapeutic dose of prednisone in children is 1 to 2 mg/kg/day and in adults is 40 to 80 mg/day.

Side Effect Profiles and Management

Despite their clear therapeutic benefits, corticosteroids are not without risk. There are many potential side effects that can develop depending in part on the route of administration, dosage used, and duration of therapy. Topical steroids (aside from the weakest such as hydrocortisone) applied to the skin can, over time, can lead to atrophy, thinning, and striae. In contrast, bronchial mucosa atrophy has not been described in patients who have used ICS in recommended doses, even for decades. Other adverse events associated with systemic steroid use include mood disturbances, diabetes mellitus, Cushing syndrome, hypertension, cataracts, muscle atrophy, and osteopenia or osteoporosis.

Measures to prevent or correct abnormalities in bone mineral metabolism

induced by oral corticosteroids or high-dose ICS require cooperative patients and physician expertise. Estrogen/progestin replacement therapy has proven value in prevention of bone loss and fractures in postmenopausal women, but its risk profile includes cardiovascular disease and breast cancer (248). It should be administered only if truly indicated. Regular gynecologic examinations are necessary. Prevention of osteopenia is of paramount importance and should begin early because bone mass increases until about 25 to 45 (or earlier) years of age and then declines over years. Exercise, sedentary lifestyle, cigarette smoking, excessive alcohol consumption, and overuse of thyroxine in euthyroid or possibly hypothyroid patients are some additional factors to address in terms of bone health. Adequate calcium intake of 1,200 mg or more for women (1,000 mg for men) and of vitamin D, 800 IU for women, is advisable. Bisphosphonates are often indicated for patients with osteopenia. Patients with established osteopenia or osteoporotic fractures may require combinations of medications in different categories, including bisphosphonates, calcitonin, parathyroid hormone (teriparatide), fluorides, selective estrogen receptor modulators (raloxifene), vitamin D, and calcium supplementation.

A potentially serious side effect from corticosteroids is suppression of the HPA axis. This results in an impaired ability to tolerate stress, and for this reason, patients must receive increased doses of corticosteroids during stressful situations, such as surgery, infectious illness, and even exacerbations of asthma. The extent of suppression, however, is variable from patient to patient. The time required for a return to normal HPA activity after discontinuation of oral corticosteroids varies and is unpredictable. In a rare patient, inability of the HPA axis to respond to stress may continue for up to 1 year after the cessation of therapy; in other patients, normal HPA reactivity may persist despite their taking corticosteroids for as long as 10 years.

Although major side effects are not usually observed in patients receiving less than 20 mg of prednisone daily (administered as a single morning dose), it remains important for corticosteroids to be used for the shortest time at the lowest dose necessary to achieve the clinical goal. A 3- to 7-day course of prednisone in therapeutic doses may be sufficient to reverse an occasional acute episode of asthma that has not responded adequately to the common modes of therapy, such as ICS and β_2-adrenergic agonists. If oral corticosteroids are required for longer periods, abrupt discontinuation may be followed by the return of acute symptoms. Until significant clearing of signs and symptoms of asthma occur, prednisone or the equivalent should be administered at a steady dosage rate over the first 1 to 2 weeks. In a small group of patients who have abruptly

discontinued corticosteroids after prolonged use, a withdrawal syndrome may occur, consisting of malaise, emotional lability, myalgia, and low-grade fever.

If patients are chronically dependent on oral corticosteroids for disease management, the physician should attempt to convert to an alternate-day regimen. One common mistake is to try to accomplish this conversion too rapidly. If a patient has been receiving split doses of prednisone on a daily basis, the first step should be to establish control of the severe asthma with a single morning dose of prednisone. Once the patient is stable, tripling the daily dose on alternate days may be adequate for control of the disease. Close patient supervision is essential during this critical changeover period. Some patients will not tolerate alternate-day steroid therapy even with very large doses of prednisone and should be managed on daily steroids using a single morning prednisone dose. The half-life of prednisolone is about 200 minutes in patients requiring daily prednisone or alternate-day prednisone, and other pharmacokinetic parameters are similar (249).

β_2-Adrenergic Receptor Agonists

Adrenergic receptors are G protein-coupled receptors important in regulating a variety of physiologic processes, including cardiac output and smooth muscle tone. The β_2-adrenergic receptor is particularly relevant in asthma because it is highly expressed in the bronchi and, upon activation, induces bronchodilation. Adrenergic drugs that possess β_2-adrenergic–stimulating activity are most effective in the treatment of asthma and, since the 1940s, numerous β_2 agonists have been developed (Table 19.10). By binding to the β_2-adrenergic receptor, these agonists can cause an increase in intracellular cyclic adenosine monophosphate (cAMP) which in turn activates protein kinase A to interact with several downstream mediators to induce smooth muscle relaxation (Figure 19.5). Although not considered "anti-inflammatory," β_2-adrenergic agonists can also increase the function of cilia in epithelial cells, decrease microvascular permeability, and facilitate the translocation of the glucocorticoid receptor from the cytoplasm into the nucleus of the cell (250).

There are several important pharmacologic properties to consider when selecting a β_2-adrenergic agonist. These medications can be either full agonists (i.e., producing a maximal response) or partial agonists (i.e., producing a less than maximal response). The efficacy of a given β_2-adrenergic agonist depends on the type and density of the β_2-adrenergic receptor present in a given organ or

tissue. Additionally, β$_2$-adrenergic agonists have varying binding affinities for other adrenergic receptors, including the β$_1$-adrenergic receptor. This selectivity is especially relevant because the activation of the β$_1$-adrenergic receptor can lead to increased cardiac contractility and heart rate. Finally, β$_2$-adrenergic agonists have also variable rates of onset and duration of their clinical effects.

Short-Acting β$_2$-Adrenergic Agonists

Short-acting β$_2$ agonists (SABAs are defined by a fast onset (5 to 10 minutes) and short duration of effect (6 hours). These agents remain the mainstay of treatment for acute bronchoconstriction and as a prevention strategy to protect against bronchoconstriction induced by exercise or other triggers, such as methacholine. However, SABAs should not be used as a regular maintenance therapy. Nevertheless, in a 16-week study of 255 patients with mild asthma, "as-needed" and "scheduled" albuterol produced similar degrees of bronchodilation and symptom control without safety signals (251). In a longer double-blind placebo controlled study of 89 patients with asthma lasting 24 weeks, only 30% of patients reported an improvement in asthma control while taking a scheduled SABA compared to 70% when using a SABA as needed for symptom relief only (252).

Additionally, there is a concern that the scheduled use of short-acting β$_2$-adrenergic agonists may potentiate an allergic response. Regular albuterol use was associated with both an increase in airway reactivity to allergen and a reduction in the protective effects observed following allergen-induced acute bronchoconstriction (253). In a separate study of 11 patients with allergic asthma, those who received 200 μg of albuterol by MDI four times daily for 1 week had a more significant reduction in FEV$_1$ (23.1%) in the late phase of allergen response following bronchoprovocation challenge than placebo-treated controls (13.2%) (254). The conclusion was that regular, scheduled use of albuterol could cause continued airway inflammation, but how much clinical effect these data have on asthma control and management remains controversial.

TABLE 19.10 β$_2$-ADRENERGIC AGONISTS FOR ASTHMA

NAME	SINGLE ENTITY FORMULATION
Albuterol	Proair HFA inhalation suspension 90 μg
	Proventil HFA inhalation suspension 90 μg
	Ventolin HFA inhalation suspension 90 μg

	Albuterol inhalation solution 0.083%, 0.5%
	Accuneb inhalation solution 0.21%, 0.42%
	Ventolin syrup 2 mg/5 mL
	VoSpire ER extended-release tablets 4 mg, 8 mg
Salmeterol	Serevent inhalation suspension 21 µg
	Serevent Diskus 50 µg
Levalbuterol	Xopenex pediatric inhalation solution 0.31 mg/3 mL,
	Xopenex inhalation solution 0.63 mg/3 mL, 1.25 mg/3 mL, 1.25 mg/0.5 mL
	Xopenex HFA inhalation suspension 45 µg
Metaproterenol	Alupent inhalation aerosol 0.65 mg
	Metaproterenol inhalation aerosol 0.4%, 0.6%
	Alupent syrup 10 mg/5 mL
	Albuterol tablets 10 mg, 20 mg
Terbutaline	Terbutaline solution for injection 1 mg/mL
	Terbutaline tablets 2.5 mg, 5 mg
Formoterol	Foradil aerolizer inhalation powder 12 µg
	Perforomist nebulizer solution 20 µg/2 mL
Fenoterol	Berotec inhalation solution 0.25 mg/mL, 0.625 mg/mL
	Berotec inhalation aerosol 100 µg
	Berotec tablets 2.5 mg
	Combinations
Albuterol/Ipratropium bromide	Combivent inhalation suspension
	Duoneb nebulizer solution

Fluticasone/Salmeterol	Advair Diskus inhalation powder 100/50, 250/50, 500/50
	Advair HFA inhalation suspension 45/21, 115/21, 230/21
Budesonide/Formoterol	Symbicort 80/4/5, 160/4.5 inhalation aerosol
Mometasone/Formoterol	Dulera 100/5; 200/5 inhalation aerosol
Fluticasone furoate/Valenterol	Breo 100/25 dry powder

Albuterol (or salbutamol) is the leading SABA and is a partial agonist of the β_2-adrenergic receptor. Albuterol is available in MDIs (ProAir HFA, Proventil HFA, Ventolin HFA), dry-powdered inhalers (ProAir RespiClic), and as an inhalation solution for nebulizers (AccuNeb). Although albuterol is available as an extended-release tablet (VoSpire ER), oral administration of β_2-adrenergic agonists is not the preferred route of treatment for asthma. The most common side effects observed with albuterol include nervousness, tremor, and palpitations and tachycardia.

The administration of albuterol inhaler or by nebulizer provides comparable bronchodilation, although larger doses of albuterol are necessary during nebulization because of the nebulizer's inefficiency (255). In adults with acute asthma, McFadden and colleagues (256) found that three 2.5 mg doses of albuterol every 30 minutes by nebulization was comparable to two 5 mg aerosolized treatments given 40 minutes apart.

Another treatment option for acute asthma involves continuously nebulized albuterol solution. For this, 7.7 mL of 0.5% albuterol is prepared in 100 mL of saline and infused by pump initially from 14 to 26 mL/hour while 100% oxygen is supplied by nebulizer. Alternatively, 15 mg albuterol can be nebulized in 60 mL of normal saline over 2 hours (257). However, studies have not demonstrated superior results with continuously nebulized albuterol compared to repeated nebulized albuterol administration or to continuously nebulized albuterol with the addition of 2 to 15 mg ipratropium bromide, an anticholinergic agent (257). For children >12 years of age and adults with episodes of acute asthma, the

recommendations of the NAEPP include two to four inhalations from an MDI every 20 minutes up to three times (3).
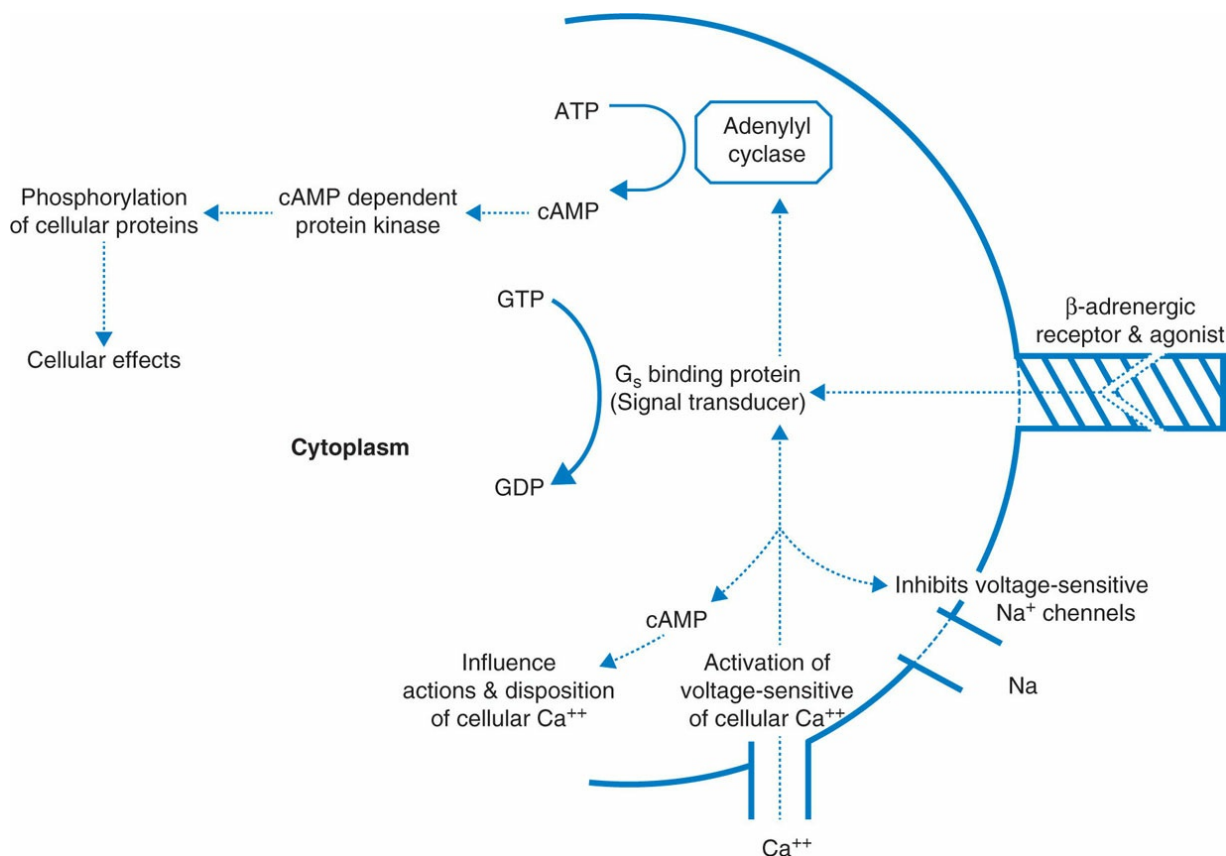
■ FIGURE 19.5 A simplified schematic of β_2-adrenergic receptor stimulation. β_2-Adrenergic agonist stimulation of its receptor causes a conformational change in the guanine nucleotide-binding regulatory protein G_S. There is increased guanosine triphosphatase (GTPase) activity and then a transduced signal, resulting in activation of adenylate cyclase. The sequence raises the concentration of cyclic adenosine monophosphate (cAMP). The regulatory protein G_S couples β_2-adrenergic receptors to adenylate cyclase and calcium channels. G_S interacts with the sodium channel, resulting in its inhibition.

Levalbuterol is the (R)-enantiomer of albuterol and was approved by the Food and Drug Administration (FDA) in 1999 for the treatment of bronchospasm in patients aged 4 years and older. It is marketed in the United States as Xopenex and is available as an MDI or nebulized solution. The pediatric and adult doses are 0.31 mg and 0.63 to 1.25 mg, respectively, and can be administered every 4 to 6 hours. Levalbuterol is about four times as potent as albuterol with 0.63 mg of levalbuterol providing comparable bronchodilation to 2.5 mg of albuterol (258). For patients who experience tremulousness and palpitations with albuterol, levalbuterol is a useful alternative, but maximal bronchodilation is

similar to that achieved with albuterol.

Older SABAs Once Used for Asthma

In addition to albuterol and levalbuterol, other SABAs include *Pirbuterol* (Maxair) and *Metaproterenol* (Alupent). However, these latter two SABAs were phased out of the US market in 2013 and 2010, respectively. Aerosolized *Terbutaline* (Bricanyl) is currently not available in the United States.

Epinephrine directly activates both α- *and* β-adrenergic receptors and has a potent bronchodilation effect. While most commonly used for the treatment of anaphylaxis, epinephrine was used extensively in the past for treatment of acute asthma. The recommended adult dose is 0.30 mL of a 1:1,000 solution administered intramuscularly. In infants and children, the dose is 0.01 mL/kg, with a maximum of 0.25 mL. The dose may be repeated in 15 to 30 minutes if necessary. Intramuscular epinephrine may still have a place for some patients with acute severe asthma who have not responded to albuterol because they are unable to inspire sufficiently or in patients with acute severe wheezing where it is not clear whether the patient with asthma is experiencing anaphylaxis. Nebulized racemic epinephrine is also effective but is not used unless the patient has an upper airway obstruction (epiglottitis or stridor).

Side effects of epinephrine include agitation, tremulousness, tachycardia, and palpitation. Hypertension in the presence of acute asthma often resolves with epinephrine administration. This occurs because of a decrease in bronchospasm and as a result of a decrease in peripheral vascular resistance by stimulation of β_2-adrenergic receptors in smooth muscle. Epinephrine must be administered with caution in patients with cardiovascular disease and hypertension but should not be considered contraindicated when bronchoconstriction is significant if albuterol is not being used. The maximum bronchodilator effect of epinephrine given intramuscularly is about equivalent to that of inhaled β_2-adrenergic agonists and occasionally in the severely obstructed patient exceeds what can be gained by aerosol therapy. Although epinephrine is an old drug, it is expedient, effective, and rapidly metabolized.

Ephedrine also stimulates both α- and β-adrenergic receptors but is less potent than albuterol and epinephrine. It has an onset of action of ˜1 hour with a peak effect between 2 and 3 hours. Ephedrine is an outdated for treatment of asthma but was used for decades because it was effective by oral administration and possessed a long duration of action (3 to 6 hours). It is available without prescription (25 to 50 mg) for asthma and as a stimulant.

In summary, short-acting β_2-adrenergic agonists currently are recommended as rescue therapy for acute asthma exacerbations and not for daily scheduled use, at least for most patients. These medications, when used properly, can also provide protection against EIB. For patients with uncontrolled asthma despite use of a SABA, a step-up therapy in therapy is indicated and, in the case of moderate-to-severe persistent asthma, the use of a combined ICS and long-acting β_2-adrenergic agonist may be indicated. In resource-poor countries or for patients in resource sufficient countries, who are not able to afford controller medications, unfortunately, their monotherapy consists of albuterol.

Long-Acting β_2-Adrenergic Agonists

As the name implies, long-acting β_2 agonists (LABAs) have a longer duration of bronchodilator effect (12 to 24 hours) and can inhibit both the early and late phases of the respiratory response following allergen challenge. These medications are recommended for administration concomitantly with an ICS. This is due to findings from a large double-blind placebo controlled trial examining the use of a LABA versus placebo as add-on therapy in patients with asthma. This study showed a small but significant association between LABA use and increased risk of asthma-related death (odds ratio 4.37), particularly among African Americans (259). Important limitations of this study included difficulties in patient enrollment, lack of in-person follow-up in a medical clinic, and no method by which medication compliance was reinforced. Further, patients received individual inhalers (salmeterol and fluticasone) but not salmeterol/fluticasone or did not use an ICS for persistent moderate-to-severe asthma.

Given these findings, a subsequent meta-analysis was performed which found an odds ratio of asthma-related death to be 2.7 and 7.3 when a LABA was prescribed with or without an ICS, respectively (260). Additionally, no deaths among 22,600 patients were reported when either a combined ICS/LABA inhaler or a corticosteroid inhaler alone was prescribed (260). In 2016, another large prospective multicenter double-blind study involving 11,679 patients with asthma reported no significantly increased risk of serious asthma-related events between patients who received a combined corticosteroid/LABA inhaler versus a corticosteroid alone (261). Furthermore, this study found those patients taking a combined ICS/LABA had significantly fewer asthma exacerbations than those patients receiving ICS alone (261).

Salmeterol is a partial β_2-adrenergic receptor agonist with an onset of action

within 20 minutes. It is 50 times more potent experimentally than albuterol but provides a similar peak bronchodilation. Salmeterol is currently marketed in the United States as Serevent and is indicated for the treatment of asthma and for the prevention of exercise-induced bronchospasm in patients aged 4 years and older. More commonly, salmeterol is prescribed in combination with the ICS fluticasone and marketed as Advair. The recommended dose of salmeterol is 50 µg twice daily.

Formoterol is a full β_2-adrenergic agonist with a rapid onset of action within 5 minutes. It has a maximum bronchodilator effect similar to salmeterol or albuterol administered every 6 hours. Until 2016, formoterol was available as a monotherapy inhaler Foradil but has since been withdrawn from the market. However, this LABA is found in combination with the ICS mometasone or budesonide and marketed as Dulera or Symbicort, respectively. The recommended dose of formoterol is 9 to 10 µg twice daily. Although not approved in the United States as a reliever medication, the combined budesonide/formoterol is used in other countries for both acute and maintenance therapy (262–264). The nebulized form of formoterol, Performomist, is not currently approved for the treatment of asthma.

The use of a LABA does not preclude the use of a SABA. Responses of FEV_1 to albuterol were preserved for 6 hours despite regular use of salmeterol (265). Such patients should receive ICS therapy, but even in its absence, in this study, a diminished response to successive doses of albuterol (or tachyphylaxis) did not occur (265). Thus, patients with moderate or severe persistent asthma may require a scheduled LABA and intermittent albuterol or other SABA to control their disease.

In summary, data support the use of regularly scheduled long-acting β_2-adrenergic agonists with ICS for moderate and severe persistent asthma (266,267). In patients whose asthma is not well controlled on low-dose ICS, studies have shown the combination of an ICS plus 12-hour long-acting β_2-adrenergic agonist provides better asthma control than solely increasing the dose of the corticosteroid (268). As patients improve, it is possible that less or no β_2-adrenergic agonist can be used. Alternatively, full control may still not be achievable despite combined ICS/LABA therapy, and additional therapeutic agents should be considered.

Ultra-Long-Acting β_2 Agonists

Ultra-LABAs represent the newest class of β_2-adrenergic receptor agonists.

These medications are more lipophilic than prior agents and thus have a longer duration of action (24 hours). Similar to LABAs, ultra-LABA monotherapy is not recommended for the treatment of asthma, but select ultra-LABAs (e.g., Indacaterol and Olodaterol) are approved as single maintenance therapy in COPD.

Vilanterol is a partial β_2-adrenergic receptor agonist with a rapid onset of action within 5 minutes. It has a greater potency than albuterol and salmeterol but is comparable to formoterol (269,270). Vilanterol is available in combination with Fluticasone furoate and marketed in the United States as Breo. This medication is indicated for the treatment of asthma in patients aged 18 years and older and is administered as 1 inhalation (of 25 µg of vilanterol) daily.

In summary, an ultra-LABA in combination with ICS provides another treatment option in the management of patients with moderate-to-severe persistent asthma. Although this combined medication can significantly improve FEV_1 in patients with asthma compared to placebo, it remains unclear whether it is more efficacious than combined ICS and other LABAs (271).

Genetic Polymorphisms and the β_2-Adrenergic Receptor

As with most clinical observations, there is significant variability in patient responses to β_2-adrenergic agonists. This has led to studies of SNPs at the 16 and 27 positions of the gene encoding the β_2-adrenergic receptor (located on chromosome 5q31). Most patients with mild asthma have the Glycine/Glycine genotype at the 16th amino acid position of the β_2-adrenergic receptor, and such patients have a better response to β_2-adrenergic agonist therapy compared with patients who have the Arginine/Arginine genotype (272,273). This finding has not been replicated large studies of patients treated with salmeterol alone or the combinations of either formoterol/budesonide or salmeterol/fluticasone (274,275). Thus, although there are differences in responses to short-acting β_2-adrenergic agonists, additional investigations are needed to understand therapeutic differences and how to provide "personalized" pharmacotherapy.

Adverse Effects of β_2-Adrenergic Receptor Therapy

The immediate relief of short-acting β_2-adrenergic agonists has made them widely acceptable to both patients and physicians. Unfortunately, some patients develop an almost addictive relationship with their inhalers, which results in excessive use and risk of arrhythmias and death (276). Physicians, other health care providers, and pharmacists need to be aware of the potential overuse of

MDIs, dry-powder inhalers, and/or nebulizers by patients and the potential "masking" of a deteriorating underlying disease. Unlimited or unsupervised prescription refills cannot be recommended because when asthma is worsening, patient self-management may result in a fatality.

As an asthma attack progresses and continued β_2-adrenergic agonist therapy is used in the absence of inhaled or oral corticosteroids, there may be development of arterial hypoxemia, carbon dioxide retention, and acidosis not recognized by the patient. Although subjective and objective improvement of airway obstruction is produced by inhaled short-acting β_2-adrenergic agonists, the associated hypoxemia of asthma is not improved and may be increased. This phenomenon results from enhancing the already existing V/Q imbalance by either increasing aeration of those alveoli already overventilated in relation to their perfusion or by reestablishing ventilation to nonperfused alveoli. The resultant hypoxemia is usually clinically insignificant, unless the initial PO_2 is on the steep portion of the oxygen–hemoglobin dissociation curve (i.e., less than 60 mm Hg). In moderately severe acute asthma, oxygen should be administered to correct the hypoxemia.

Another concern with inhaled β_2-adrenergic agonists is the occasional paradoxic response of increased bronchial obstruction. With an exacerbation of asthmatic symptoms, these patients may overuse inhalation therapy because of a decreasing response to preceding inhalations. A cycle begins of increasing obstruction with increasing use of the aerosol. This pattern may progress to acute severe asthma or respiratory/cardiac arrest. Patients identified as using β_2-adrenergic agonist inhalation or nebulizers excessively should have this therapy terminated or monitored more aggressively. The physician should begin a short course of prednisone to control underlying bronchoconstriction and airway inflammation. There remains a public health concern of asthma fatalities that occur in patients with persistent asthma, who rely on short- or long-acting β_2-adrenergic agonists in the absence of ICS or other controller therapy.

Muscarinic Antagonists

Muscarinic receptors are G protein-coupled receptors that bind acetylcholine and play a prominent role in the parasympathetic nervous response. There are five different muscarinic receptors with M_1, M_2, and M_3 being the most common subtypes found in the respiratory tract. M_1 and M_3 receptors are present on airway smooth muscle and, upon engagement, elicit bronchoconstriction. In

contrast, signaling through M_2 receptors on airway smooth muscle can inhibit acetylcholine release and thus reduce cholinergic-mediated bronchoconstriction. Thus, the optimal anti-cholinergic drug used for asthma treatment would have a high affinity for M_1 and M_3 receptors (to block bronchoconstriction) but a low affinity for the M_2 receptor (to promote its inhibitory effects). In addition to varying receptor affinities, anticholinergic agents can differ by rate of onset and duration of clinical effect.

Short-Acting Muscarinic Antagonists

Ipratropium Bromide (Atrovent) is a nonselective antagonist of the M_1, M_2, and M_3 receptors with a duration of effect lasting approximately 2 to 4 hours. However, ipratropium bromide is not recommended as monotherapy for the treatment of acute asthma, given it has a slower onset of action and a smaller clinical effect than β_2-adrenergic agonists. Additionally, a large meta-analysis found no clinically significant benefit when using either an anticholinergic agent alone or in combination with a β_2-adrenergic agonist for the management of chronic asthma (277). In contrast, separate studies have found the use of an anticholinergic together with a β_2-adrenergic agonist to improve lung function and reduce hospitalizations during acute asthma exacerbations (278,279). Dual combined ipratropium bromide plus albuterol is currently available in an MDI (Combivent) and nebulized (Duoneb) formulations.

Long-Acting Muscarinic Antagonists

Tiotropium Bromide (Spiriva, Spiriva Respimat) is a higher affinity muscarinic receptor antagonist than Ipratropium Bromide. While it binds equally to both the M_2 and M_3 receptors, tiotropium has a much slower dissociative rate from the M_3 receptor, thus prolonging its bronchoprotective effects. This medication is currently indicated in patients aged 12 years and older with a recommended dose of 2.5 μg once daily.

In a large, randomized three-way, double-blind crossover study, the additive effect of tiotropium was compared to the additive effect of a LABA as well as to the doubling effect of the corticosteroid dose among patients with uncontrolled moderate persistent asthma taking inhaled glucocorticoids (280). This study found patients who received tiotropium in addition to their glucocorticoid had a significant improvement in lung function and symptoms compared to patients who received an increase in steroid dose alone (280). Additionally, there was a noninferior improvement compared to patients who received both a LABA and

glucocorticoid (280). In more recent meta-analyses, the addition of a LAMA was found to improve lung function and reduce the rate of asthma exacerbations among patients taking inhaled glucocorticoids without LABA (280) as well as reduce the need for rescue oral steroids in patients already taking both a LABA + ICS (281,282).

Leukotriene Antagonists and Biosynthesis Inhibitors

Cysteinyl leukotrienes are derived from arachidonic acid and include Leukotriene C_4 (LTC_4) which is converted to LTD_4 which is then converted to Leukotriene E_4 (LTE_4). These lipid mediators, in particular LTC_4 and LTD_4, are potent inducers of bronchoconstriction and thus are thought to contribute to asthma pathogenesis. There are three cysteinyl leukotriene receptors aptly named cysteinyl leukotriene receptor-1 ($CystLT_1R$), -2 ($CystLT_2R$), and -3 ($CystLT_3R$). Each leukotriene has a different affinity for a given receptor with LTD_4 having the highest affinity for the $CysLT_1R$. LTD_4 and LTC_4 share a similar high affinity for the $CysLT_2R$ and LTE_4 has the highest affinity for the more recently discovered $CysLT_3R$ (283,284). There are currently no FDA–approved antagonists of either $CystLT_2R$ or $CystLT_3R$.

Leukotriene Antagonists

Montelukast (Singulair) and *Zafirlukast* (Accolate) are both $CysLT_1$ receptor antagonists approved for the prophylaxis and chronic treatment of asthma. Montelukast is indicated for patients aged 12 months and older while Zafirlukast is indicated for patients aged 5 years and older. Both leukotriene antagonists can block declines in FEV_1 from exercise, allergen challenge, and aspirin administration and serve as controller medications (285–291).

Administration of montelukast or zafirlukast in adults with persistent mild to moderate asthma resulted in a reduction in symptoms and increase in FEV_1 by up to 13%, compared with a placebo response of 4.2% (88). Comparable results were reported in children aged 6 to 14 years (88). These findings support the concept that leukotrienes contribute to airway tone. However, there is some patient-to-patient variability in the degree of FEV_1 improvement observed with montelukast. Approximately 15% of patients treated with this medication note an improvement in bronchodilation by 18% to 25%, whereas other patients only observe an 8% to 10% increase (88).

The effects of leukotriene antagonists in controlling asthma can extend

beyond bronchodilator responses (88,287). In one study, montelukast 10 mg (or placebo) was added to beclomethasone dipropionate 200 μg twice daily in adult patients with incompletely controlled asthma. This combination of montelukast and ICS was associated with a significant increase in FEV_1, decrease in asthma symptoms, and reduction in number of asthma exacerbations compared to patients treated with placebo plus ICS (291). The leukotriene receptor antagonists can help some patients with persistent asthma lower their dosage of ICS.

Leukotriene antagonists are generally well tolerated and effective (292). However, a postmarketing analysis of these medications reported an increase in neuropsychiatric episodes, including mood changes, depression, dream abnormalities, and suicidal ideations, especially among adolescents and the elderly. As a result, patients should be advised of this small, possible risk and closely monitored for any change in behavior.

Leukotriene Synthesis Inhibitor

Zileuton (Zyflo) is an inhibitor of the 5-LO enzyme and blocks the downstream conversion of arachidonic acid into leukotrienes by ˜26% to 86% (293,294). In a 12-week study of zileuton in patients with asthma, the average FEV_1 improved by 20.8% with active treatment compared to 12.7% with placebo (293). Additionally, in another study, the use of zileuton resulted in bronchodilation (14.6% vs. 0% for placebo) 60 minutes following treatment (294).

Zileuton is currently indicated for patients with asthma aged 12 years and older. Reversible elevations of alanine aminotransferase, over three times normal limits, occurred in less than 2.5% of patients and 0.5% of controls (293,294). As a result, it is recommended that liver function tests be measured while taking this medication. As with the leukotriene receptor antagonists, mood changes and other neuropsychiatric events have also been associated with Zileuton and patients should be monitored appropriately.

Biological Modifiers

Significant advances have been made in defining the cellular and molecular mechanisms contributing to asthma pathogenesis. As discussed in Chapter 1, allergic asthma is characterized by a type 2 inflammatory response with IgE as well as the cytokines IL-4, IL-5, and IL-13 all thought to play important roles. In addition to promoting inflammation, these mediators have also become important therapeutic targets for drug design. It is hypothesized that if the type 2

inflammatory response could be attenuated, asthma symptoms and exacerbation rates could be improved, and the natural history of the disease potentially altered. Currently, there are three immunomodulatory agents approved by the FDA for the treatment of moderate-to-severe allergic asthma. Additionally, the safety and efficacy of other biological modifiers inducing those that target the IL-4 receptor α chain (295), IL-13 (296), IL-5 (297,298) and TSLP (77,299) are being evaluated in ongoing clinical trials.

Anti-IgE

Omalizumab is a humanized monoclonal IgG1κ antibody that recognizes the Fc portion of IgE. Upon binding, omalizumab forms a complex with free (or unbound) IgE and prevents the IgE from engaging with its receptor, FcεRI. In a pooled analysis of over 4,300 clinical trial participants with severe asthma, omalizumab was shown to significantly reduce the rate of asthma exacerbations and ER visits by 38% and 47%, respectively (300). Additionally, patients treated with omalizumab noted a significant improvement in quality of life and were more likely to tolerate a reduction in daily ICS than placebo-treated controls (301–303).

The clinical effects observed with omalizumab may be secondary to a variety of mechanisms. By forming complexes, omalizumab can both reduce serum levels of free IgE (304) and downregulate FcεRI receptor expression on the surface of mast cells, basophils, and dendritic cells (305–307). Additionally, Omalizumab has been associated with a decrease in the number of eosinophils detected in the blood and sputum (304). Taken together, omalizumab can impair the ability of IgE to bind allergen, to activate basophils and mast cells, and to promote the development of a type 2 inflammatory response.

Omalizumab is marketed under the name Xolair in the United States and is indicated for the treatment of moderate-to-severe persistent asthma in patients aged 6 years and older. To qualify for treatment, patients must have at least one positive skin test or *in vitro* confirmed specific IgE to a perennial allergen and have asthma symptoms that are inadequately controlled with ICS. This medication is administered subcutaneously with the dose (75 to 375 mg) and frequency of administration (every 2 or 4 weeks) determined by the patient's body weight and total IgE level prior to treatment. Because omalizumab causes serum levels of total IgE (a measurement of both free and bound IgE) to increase (308,309), it is not recommended that total IgE levels be monitored while on treatment (this point applies to some but not all *in vitro* assays to detect total IgE).

Importantly, postmarketing analyses found an increased risk of anaphylaxis occurring in 0.2% of patients receiving omalizumab. Symptoms developed as soon as 90 minutes after the administration of the first dose of omalizumab and as late as 1 year into treatment. Due to these observations, patients should be properly counselled, prescribed auto-injectable epinephrine, and, after receiving omalizumab, monitored closely for 2 hours after the first three injections and 30 minutes after subsequent injections in a health care setting equipped to manage severe allergic reactions (310). Finally, a recent large observational cohort study found no association between omalizumab and an increased risk of malignancy (311).

Anti–IL-5

Mepolizumab is a humanized monoclonal IgG1κ antibody that binds to soluble IL-5, thereby preventing IL-5 from engaging with and activating its receptor, the IL-5 receptor. IL-5 is a critical cytokine for eosinophil survival, activation, and proliferation. By antagonizing the effects of IL-5, mepolizumab has been shown to reduce peripheral blood eosinophils (312–314). In phase 3 randomized double-blind placebo controlled trials of patients with asthma, mepolizumab was associated with a significant reduction in clinically significant asthma exacerbations compared to placebo (312,313). However, significant associations between the use of mepolizumab and improvements in either FEV_1 or asthma symptoms were variable (312,313). In a separate study, the dose of oral glucocorticoids was 2.39 times more likely to be reduced (and by a median of 50%) in patients with asthma receiving mepolizumab as compared to placebo (315). Importantly, despite the reduction in oral steroids, mepolizumab treated patients still noted a 32% relative reduction in annual rate of exacerbations (315). The mechanisms by which mepolizumab exerts its clinical effects and by which a reduction in eosinophils can lead to a decline in asthma exacerbations remain under investigation.

Mepolizumab is marketed under the name Nucala in the United States and is indicated for the treatment of severe persistent asthma in patients aged 12 years and older. To qualify for treatment, patients must have both asthma symptoms that are inadequately controlled with ICS and an eosinophilic phenotype associated with their disease. The peripheral blood eosinophil count should be ≥150 cells/µL within 6 weeks or ≥300 cells/µL within 1 year prior to starting treatment. Mepolizumab is administered subcutaneously at a dose of 100-mg every 4 weeks and is not based upon a patient's weight (or IgE concentration). To date, there have been no reported episodes of anaphylaxis with mepolizumab

but two patients (compared to 0 placebo-treated controls) developed shingles during the course of the clinical trials. Varicella vaccination should be considered, if medically appropriate, prior to starting mepolizumab.

Reslizumab is a humanized monoclonal IgG4κ antibody that, like mepolizumab, binds to soluble IL-5, thereby preventing it from engaging with and activating the IL-5 receptor. Large double-blind placebo controlled clinical trials have shown that in patients with moderate-to-severe persistent asthma with uncontrolled disease reported significant reductions in asthma exacerbations as well as improvements in lung function and quality of life with reslizumab compared to placebo (316–318). The clinical efficacy of reslizumab compared to Mepolizumab cannot be evaluated at this time, given that there have been no direct head-to-head clinical studies.

Reslizumab is marketed under the name Cinqair in the United States and is indicated for the treatment of severe persistent asthma in patients aged 18 years and older. To qualify for treatment, patients must have asthma symptoms that are inadequately controlled with ICS and have an eosinophilic phenotype associated with their disease. The peripheral blood eosinophil count should be ≥400 cells/ µL in the 3 to 4 weeks prior to starting treatment. Reslizumab is administered intravenously over a period of 20 to 50 minutes at a dose of 3 mg/kg every 4 weeks. Anaphylaxis was reported in 0.3% of patients receiving Reslizumab and occurred as early as during the second infusion. It is thus recommended that patients be properly counselled, prescribed injectable epinephrine for emergency use, and, after receiving Reslizumab, monitored closely in a health care setting equipped to manage severe allergic reactions.

Theophylline (1,3-dimethylxanthine) is a methylxanthine drug that remains a third-line treatment option for ambulatory or hospitalized patients with moderate-to-severe persistent asthma. The limited use of this drug is secondary to its narrow therapeutic index, major side effects, and significant interactions with numerous other medication classes (see Chapter 36). The most important pharmacologic action of theophylline is bronchodilation but other properties include central respiratory stimulation, inotropic and chronotropic cardiac effects, diuresis, relaxation of vascular smooth muscles, improvement in ciliary action, and reduction of diaphragmatic muscle fatigue.

The molecular mechanisms by which theophylline exerts its clinical effects remain unclear. It has been shown *in vitro* to increase cAMP concentrations by inhibiting phosphodiesterase, the enzyme that converts 3′5′-cAMP to 5′-AMP. However, the inhibition of phosphodiesterase by theophylline was accomplished

with concentrations that would be toxic *in vivo*; thus, theophylline's mechanism of action is unlikely attributable to phosphodiesterase inhibition. Possible alternative explanations for bronchodilation induced the antagonism of adenosine receptor, inhibition of the pro-inflammatory cytokine NF-κB, and induction of the anti-inflammatory cytokine, IL-10 (319).

Optimal bronchodilation from theophylline is a function of the serum concentration. Maximal bronchodilation is usually achieved with concentrations between 8 and 15 µg/mL. However, some patients achieve adequate clinical improvement with serum theophylline levels at 5 µg/mL or even lower. The explanation for this phenomenon is that the bronchodilator effect of theophylline, as measured by percentage increase in FEV_1, is related to and fairly dependent on the logarithm of the serum-level concentration (320,321). In this study, the mean improvement in FEV_1 was 19.7% with theophylline concentration 5 µg/mL, 30.9% at 10 µg/mL, and 42.2% at 20 µg/mL. At these concentrations, improvement in pulmonary function occurs in linear manner with the log of the theophylline concentration. However, using an arithmetic scale on the abscissa, improvement in pulmonary function occurs in a hyperbolic manner. Thus, although continued improvement occurs with increasing serum concentrations, the incremental increase with each larger dose decreases. About half of the improvement in FEV_1 that is achievable with a theophylline concentration of 20 µg/mL is reached with concentration of 5 µg/mL, and 75% of the improvement is reached with a concentration of 10 µg/mL.

Since the introduction of inhaled glucocorticoids, LABAs, and biologic modifiers, theophylline remains an alternative controller medication for use in patients with moderate and severe persistent asthma (3,4). When added to ICS plus β_2-adrenergic agonist combinations, theophylline may provide no additional benefit. As a result, theophylline remains indicated only in problem-patients with persistent severe asthma, steroid-phobic patients, patients with asthma and COPD, and perhaps patients who cannot afford ICS/LABA.

Chromones

Chromones are distinct chemical compounds with unique pharmacologic properties used in the treatment of various allergic diseases. These compounds stabilize mast cells, thus decreasing the release of inflammatory mediators such as histamine. Chromones also function by inhibiting IgE production and modulating sensory nerves, the latter of which has been shown to reduce the severity of itch. Chromones act directly on the mucosal surfaces but have

minimal effect in the skin. These medications are neither systemically absorbed nor metabolized.

The two major chromones, *Cromolyn* and *Nedocromil*, were once available as inhalers. However, both of these medications were taken off the US market prior to 2014 because they contained chlorofluorocarbons. Currently, cromolyn is available in oral (Gastrocrom), nasal (NasalCrom), and ophthalmic (Opticrom) formulations, whereas nedocromil is available in an ophthalmic solution (Alocril). Although these formulations are indicated for allergic rhinitis, allergic conjunctivitis, and mastocytosis, they are not recommended for treatment of acute or chronic asthma.

Formerly, inhaled cromolyn sodium was shown to be effective in preventing bronchospasm from inhaled allergens and exercise with study patients reporting a 28% to 33% reduction in asthma symptoms after administration when compared to placebo (322) (see Chapter 36). However, a Cochrane analysis found little to no improvement over placebo for maintenance therapy in children (323). Additionally, in the Childhood Asthma Management Program, nedocromil and cromolyn (as with budesonide) did not appear to protect against loss of FEV_1/FVC in mild-to-moderate asthma (324). However, cromolyn and nedocromil have been of value for prevention or minimization of EIB when inhaled up to 2 hours prior to exercise (325). Preexposure cromolyn by inhalation can help reduce symptoms triggered by animal danders, molds, high dusty environments, odors, and exercise.

Practical Considerations for Asthma Therapies

Despite the significant pharmacologic advances in asthma management, no medication will provide significant benefit if used improperly. For example, correct inhaler technique is essential for the appropriate delivery of medication. If not properly educated, patients may fail to fully expire before actuating their inhaler. Alternatively, patients may inhale too rapidly, take a submaximal inspiration, flex the neck during inspiration, and/or not hold their breath for 10 seconds after a full inspiration. In addition to improper breathing techniques, difficulties manipulating the device itself (i.e., forgetting to shake the canister before actuation, activating the inhaler twice for one inhalation, forgetting to remove the cap before inhalation) can also impact drug delivery and explain poor therapeutic responses. To address these concerns, clinicians are encouraged to review proper inhaler techniques at office visits and have the patient in turn demonstrate correct use.

A number of devices have been developed in an effort to improve the dynamics of aerosol administration by a pressurized inhaler (see Chapter 37). These devices attempt to minimize aerosol deposition in the oropharynx and increase delivery to the airways. By necessitating a slower inspiration, more drugs may be distributed to obstructed peripheral airways than with a rapid inspiration, which favors central airway deposition at the expense of the peripheral airways. Additionally, these devices can assist when effective synchronization of inhalation with actuation of the air inhaler cannot be corrected.

Motor-driven nebulizers do not result in greater bronchodilation than that achieved with pressurized metered-dose aerosol canisters. Drug delivery by motor-driven nebulizers has been considered more efficacious because the patient inhales a relatively large concentration of drug from the nebulizer. For example, the dose of albuterol added to the nebulizer is 5 mg, which is 56 times the dose generated by the MDI (90 µg). However, it was demonstrated that perhaps only 15% to 20% of the drug is actually nebulized during inspiration, and only 10% of the nebulized dose would reach the bronchi. In conclusion, the dose delivered to the lung from the nebulizer may be approximately similar to that given by a pressurized aerosol canister. Nebulizers can still provide benefit especially because they do not necessitate the patient to learn correct inhalation technique as required for inhalers.

Physicians and other health care providers should become familiar with the proper use of the different asthma devices available and, when appropriate, consider spacers and/or breath-activated units to improve drug delivery. It is advisable to recheck the patient's inhaler technique periodically because technical errors can still occur. Additionally, other barriers to medication adherence should be addressed on a more personalized basis (326). Financial costs, social factors, fear of side effects, intensity of the dosage regimen, and the patient's perception of their disease may all play important roles on how (and when) patients utilize medical therapies for the treatment of their disease.

Drugs to Use Cautiously or to Avoid

Monotherapy of persistent mild, moderate, or severe asthma with short- or long-acting β_2-adrenergic agonists is not recommended (3) and should not be done. Additionally, the use of β_2-adrenergic antagonists may enhance or trigger wheezing in overt and latent asthmatic patients. Should selective or nonselective β_2-adrenergic antagonists be required in a patient with asthma, cautious

increases in dose with close supervision is recommended. Both cardioselective (atenolol and metoprolol) and nonselective (propranolol, carvedilol, lebatalol, and timolol) blockers have been associated with increased numbers of emergency department visits and hospitalizations in patients with asthma (327). Acute bronchospasm has been associated with conjunctival instillation of timolol for glaucoma (328). Bronchoconstriction has also been described for betaxolol, a β_1-adrenergic antagonist, which is less likely to cause declines in FEV_1 than timolol (329). Occasionally, parasympathomimetic agents, such as pilocarpine, administered in the conjunctival sac can cause bronchospasm. It is advisable to make certain that the patient with persistent asthma is first achieving adequate control of asthma, such as with ICS or β_2-adrenergic agonist/ICS or other medications, so that any possible effects from necessary ophthalmic drugs are minimized.

Angiotensin-converting enzyme (ACE) inhibitors have been associated with cough and asthma (in addition to pharyngeal or laryngeal angioedema), even after the first dose (330,331). Discontinuation of the ACE inhibitor is associated with resolution of cough over several days or up to a month. ACE inhibitors and angiotensin receptor blockers antagonists are not contraindicated in patients with asthma in the absence of prior adverse reactions, such as cough or acute angioedema.

Narcotics analgesics, such as morphine, oxycodone, hydromorphone, and fentanyl, are at least relatively (or absolutely) contraindicated during exacerbations of asthma. Moreover, morphine can activate mast cells to release histamine. Nocturnal reductions in PO_2 occur regularly in normal subjects and in patients with asthma. Acute severe asthma (status asthmaticus) is a contraindication for the use of soporific medications.

Antidepressants of the tricyclic or serotonin reuptake inhibitor classes can be continued with asthma medications. Antidepressants of the monoamine oxidase inhibitor class can be utilized but are not recommended in a patient who might receive epinephrine because there could be a severe hypertensive crisis.

Drugs possessing anticholinesterase properties may potentiate wheezing. This results from their parasympathomimetic-enhancing effect caused by the inhibition of acetylcholine catabolism. These drugs represent the primary drug treatment of myasthenia gravis; if asthma coexists, a therapeutic problem arises. When anticholinesterases are necessary, maximal doses of β_2-adrenergic agonists and ICS may be necessary. The addition of oral corticosteroids may be

indicated for more adequate control of asthma, but it must be remembered that, in some patients, myasthenic symptoms may initially worsen with addition of oral corticosteroids (332).

Nonpharmacologic Treatment

Allergen Avoidance

For those patients with allergic asthma, specific allergy management must be included in their treatment regimen. In adults, inhalant allergens are the most frequent causative agents. Many, but not all, studies suggest that there is a dose–response relationship between allergen exposure and development of asthma. Moreover, there are suggestions that there are threshold levels of allergen exposure, below which sensitization and, therefore, allergic asthma are unlikely to occur. For a major dust mite allergen *Der p* 1 it is 2 µg/g dust and for a major cockroach allergen *Bla g* 1, it is 1 unit/g dust.

When one allergen is the primary cause (e.g., animal dander) and can be removed from the environment, symptomatic relief is achieved, often within 1 to 2 months (or longer) if there is thorough cleaning. Most allergic patients, however, are sensitive to more than one allergen, and many allergens cannot be removed completely. As a result, certain strategies are recommended for avoidance of particular agents.

To reduce dust mite allergen, certain basic environmental controls in the house are advisable (333). Hypoallergenic pillows are preferred and should be enclosed in impermeable encasings. Box springs and mattresses should similarly be enclosed. Relative humidity inside the home should be between 35% and 50% to decrease dust mite growth. Bedding should be washed weekly in warm water. In some situations, additional cleaning and/or removal of carpets is beneficial because the carpet is a reservoir of dust mite allergen. For the highly dust-allergic patient, appropriate filters (i.e., high-efficiency particular air filters) on furnaces and vacuums as well as air cleaners should be used and maintained properly. The use of acaricides to eliminate dust mites, however, has limited efficacy.

In patients with perennial symptoms, it is generally advisable that pets (e.g., cats, dogs, and birds) be removed from the house if there are symptoms from contact or if there is a positive skin test.

As stated earlier in this chapter, cat dander (*Fel d* I) antigen may require months for levels to fall below threshold levels (< 8 µg *Fed d 1* /mg dust) once

the cat is removed from the household (177). Often, patients will not remove the pet as advised and instead, the physician and patient must rely on pharmacologic therapies. Washing pets weekly can reduce, albeit temporarily, pet allergen levels (334).

Other aspects may be considered with regard to the environmental control in the home. Basement apartments, because of increased moisture, are most likely to have higher levels of airborne fungi and mite antigens. Visible molds should be removed and, depending on the severity of asthma or difficulty in achieving adequate control, cleaning of the heating-ventilation-air conditioning ducts should be performed. Measures to reduce exposure to rodent urine and cockroaches should be implemented and likely require continued effort (13,335).

Ingestion of foods essentially is never the cause of asthma; an exception occurs when the cause is acute severe bronchoconstriction from anaphylaxis. Patients, however, may attribute their respiratory symptoms to aspartame or monosodium glutamate although such associations are not justified. Exposure to sulfur dioxide from sodium or potassium metabisulfite (used as an antioxidant in foods) can cause acute respiratory symptoms in patients with asthma. However, patients with stable asthma who are managed by anti-inflammatory medications will not be affected significantly by metabisulfite. But air pollution, including smoke and ash that has blown hundreds of miles from the source, can cause worsening control of asthma.

Immunotherapy

When environmental control is either impossible or insufficient to control symptoms in mono- or polysensitized patients with allergic asthma, subcutaneous allergen immunotherapy should be considered (see Chapter 13). Efficacy in asthma has been documented for pollens, dust mites, and *Cladosporium* species (336,337), and allergen immunotherapy should be considered in patients with persistent asthma, who are also being treated with pharmacotherapy (3) (Table 19.6). Other than very modest effects, subcutaneous immunotherapy with cat dander extracts has not been impressive in reducing symptoms when the cat remains in the home environment. While some studies have suggested the sublingual immunotherapy (SLIT) may reduce asthma symptoms (338), SLIT is not currently a recommended treatment option for asthma, and additional studies are needed to further investigate this indication.

Johnstone and Dutton (339), in a 14-year prospective study of subcutaneous allergen immunotherapy for asthmatic children, reported that 72% of the treated group were free of symptoms at 16 years of age, as compared with only 22% of

the placebo group. This publication occurred in 1968 and, for decades, was treated with healthy skepticism. In 2007, somewhat similar data were reported again, in that children with rhinitis who received allergen immunotherapy had less emergence of asthma those patients who did not receive allergen immunotherapy (340).

Bronchial Thermoplasty

Bronchial thermoplasty involves the delivery of targeted thermal energy directly into the airways to ablate smooth muscle and thus attenuate bronchoconstriction. The procedure is performed by bronchoscopy and divided into three treatment sessions (bronchoscopy) that specifically target the right lower lobe, then left lower lobe, and finally bilateral upper lobes of the lungs. It is currently approved for the treatment of uncontrolled severe persistent asthma despite ICS/LABA in patients aged 18 years and older.

During the bronchial thermoplasty treatment period, a transient worsening of asthma symptoms in some patients occurred (341–343). However, following this period, studies have reported variable clinical outcomes. In one instance, lung function as measured by mean FEV_1 was not significantly different between bronchial thermoplasty and controls, but subjective asthma symptoms did improve with the former treatment (342). In a second unblinded trial, bronchial thermoplasty was associated with a significant increase in FEV_1 and reduction in rescue inhaler use (341). Finally, in a large double-blind randomized control study, patients who received either bronchial thermoplasty or a sham procedure both noted improvements in asthma symptoms, but only those who received active treatment reported a significant reduction in asthma exacerbations and ER visits (344).

Given these findings, there may be certain patients for whom bronchial thermoplasty will be beneficial. Yet, there is currently no biomarker available to predict who these patients may be. Furthermore, the studies above excluded patients with FEV_1 less than 50% or had frequent asthma exacerbations, and thus the efficacy of bronchial thermoplasty in patients with severe asthma or those who are corticosteroid-dependent remains unknown. After 5 years, patients who received bronchial thermoplasty had stable lung function but continued to report lower rates of severe asthma exacerbations than prior to treatment (344). These suggest bronchial thermoplasty is well tolerated after the initial treatment period but longer follow-up studies are still indicated to monitor for any adverse effects.

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Nonallergic Asthma

Treatment of nonallergic asthma primarily involves the judicious use of pharmacologic therapy as avoidance measures; immunotherapy and immunomodulator treatments are not indicated. The next three paragraphs apply to allergic asthma as well.

Convincing evidence is available that virus-induced upper respiratory infections initiate exacerbations of asthma. Important agents for children 0 to 5 years of age include rhinovirus, RSV, parainfluenza virus; for older children and adults, influenza virus, parainfluenza virus, and rhinovirus are important. Adenovirus infection rarely acts to initiate asthma attacks. Additional viruses will be understood better (metapneumoviruses) or identified that are associated with episodes of asthma.

Mycoplasma pneumoniae infections may be associated with new-onset asthma (345) or likely exacerbations of established asthma (346). In patients with acute exacerbations of asthma, in which serologic evidence of infection with *M. pneumoniae* or *Chlamydophilia* (formerly *Chlamydia*) *pneumoniae* was present, the macrolide, telithromycin, reduced symptoms (40% vs. 27%) but did not improve PEFR significantly more than placebo (78 vs. 67 L/minute) (346). It remains to be established whether there will be an indication for macrolides for treatment of asthma, for example, whether there is an anti-inflammatory or anti-infective role because data have been disappointing for cough (347) and asthma (348).

Annual influenza vaccination should be administered according to the Centers for Disease Control and Prevention recommendations for children and adults. Treatment of secondary bacterial infections, such as acute (purulent) bronchitis and rhinosinusitis, is desirable. Pneumococcal vaccine can be administered to adults over the age of 50 years with persistent asthma, although pneumococcal pneumonia is an infrequent occurrence.

Aspirin-Exacerbated Respiratory Disease (Aspirin-Intolerant Asthma)

Treatment of aspirin-exacerbated respiratory disease (aspirin-intolerant asthma) includes avoidance measures for patients with IgE-mediated triggers of asthma, anti-inflammatory therapy, and management of CRS. It is important to avoid

aspirin and nonselective NSAIDs, which may also produce serious acute bronchoconstriction. Patients must be informed that numerous proprietary mixtures contain aspirin, and they must be certain to take no proprietary medication that contains acetylsalicylic acid. Acetaminophen may be used as a safe substitute for aspirin in nearly all patients, and other salicylates, such as sodium salicylate, choline magnesium trisalicylate, or salsalate, can be taken safely. Other patients respond with urticaria, angioedema, or anaphylaxis. The mechanisms of acute bronchoconstriction include the blockade of cyclooxygenase-1, reduced production of PGE_2, and generation of LTC_4 and LTD_4. Patients with aspirin-exacerbated respiratory disease have increased baseline urinary concentrations of LTE_4, a marker of 5-LO products. After aspirin ingestion, there is even greater increase in urinary LTE_4 concentrations, consistent with synthesis of the potent agonist LTD_4. Although PGE_2 can be thought of as a bronchodilator, it has a major role in "braking" the production of leukotrienes via inhibitory effects on 5-LO and FLAP. PGE_2 also stabilizes mast cells, but this protective effect is also reduced after aspirin ingestion. The cyclooxygenase-2 inhibitors are tolerated uneventfully (349). There are very few patients who experience acute bronchoconstriction from both cyclooygenase-1 and cyclooxygenase-2 antagonists.

In some situations, provocative dose testing with either aspirin or NSAIDs may be carried out to confirm the diagnosis or to treat underlying aspirin-exacerbated respiratory disease. Because the mean provoking dose of aspirin was 62 mg during oral challenges (350), the physician or proficient health care professional should be in attendance at all times because of the explosiveness and severity of these reactions, primarily when the initial dosage is the full dose. The FEV_1 should be at least 70% before the challenge. Pulmonary function parameters and vital signs should be measured prospectively because the patient can begin wheezing abruptly and drop the FEV_1 by 30% to 40%. Aspirin should be administered in serial doubling doses, beginning with 30 mg (It may be advisable to begin with 3 to 10 mg in some patients. Indeed, the 3 mg dosage could serve as an active placebo in very anxious patients). The dosage is advanced to 60, 100, 150, 325, and 650 mg every 3 hours if there is <20% decrease in FEV_1 with each dosage. If 650 mg of aspirin has been given and there is not a 20% decrease in FEV_1, it is unlikely that aspirin is significant in the patient's condition. When a decrease in FEV_1 of 20% occurs, the provoking dose is repeated every 3 to 24 hours until no bronchospastic response occurs. There may be long-term benefit in patients who undergo successful "aspirin

desensitization" followed by daily aspirin treatment, acknowledging that some patients will experience gastritis or gastric bleeding.

Conversion ratios between aspirin and NSAIDs are as follows: aspirin 325 mg = ibuprofen 200 mg = naproxen 220 mg = indomethacin 25 mg (350). It has been suggested that, in this context, acetaminophen of 1,000 mg may be equivalent.

Formerly, there was a notion that tartrazine intolerance/sensitivity might coexist with aspirin-exacerbated respiratory disease. However, this issue appears to be nonexistent. Should a challenge have to be perfomed to exclude tartrazine intolerance/sensitivity, begin test dosing FD&C Yellow No. 5, begin 1, 5, 15, and 29 mg every hour and monitor respiratory status and FEV_1.

Potentially (Near) Fatal Asthma

The diagnosis of potentially (near) fatal asthma is helpful because it identifies high-risk patients who are more likely to die from asthma (92,152,154). Despite aggressive intervention, such as early and intensive pharmacotherapy, allergen avoidance, and psychologic evaluation, death may occur. For some patients, using practice parameters may not be sufficient to prevent the death. Potentially (near) fatal asthma patients do not have an inexorably fatal condition, in that stabilization and clinical improvement can occur if patients are managed effectively and are compliant with office appointments and other factors. Some patient factors that complicate care of potentially (near) fatal asthma and result in noncompliance include psychologic or psychiatric conditions (schizophrenia, bipolar disorder, and personality disorders), chaotic dysfunctional family, denial, anger, lack of insight, ignorance, and child abuse by proxy. In the latter situation, some parents refuse to permit essential medications such as prednisone to be administered to their children despite previous episodes of respiratory arrest or repeated status asthmaticus. Some physician- or health care provider–related factors that can contribute to ineffectively managed patients and potential fatalities include (a) lack of appreciation for limitations in effectiveness of β_2-adrenergic agonists, leukotriene modifiers, theophylline, and combinations in increasingly severe asthma; (b) fear of prednisone; (c) failure to increase the dosage of prednisone or to administer prednisone when asthma exacerbations occur, such as during an upper respiratory tract infection; (d) lack of availability; (e) excessively demanding regimens; and (f) limited understanding of importance of a quiet chest on auscultation in severely dyspneic patients.

In survivors of episodes of nearly fatal asthma, defined as acute respiratory

arrest, presentation with PCO_2 of at least 50 mm Hg, or impaired level of consciousness, blunted perception of dyspnea has been demonstrated when patients were hospitalized, but these abnormalities normalized or improved considerably. Similarly, the ventilatory response to inhalation of carbon dioxide was not different from that of other patients with less severe asthma or nonasthmatic subjects. However, abnormal respiratory responses to decreases in inspired oxygen have been identified. This group of patients with potentially fatal asthma does not demonstrate persistent physiologic abnormalities that identify them as having intrinsically precarious asthma.

Potentially fatal asthma can be treated with ICS, inhaled β_2-adrenergic agonists, and usually alternate-day or rarely daily prednisone in compliant patients. It is advisable to institute the nonspecific general areas of care discussed previously. In contrast, in patients with malignant, potentially fatal asthma, depot corticosteroids (Depo-Medrol) can be administered after appropriate documentation is made in the medical record and the patient is informed. As for other types of asthma, prevention of fatalities and acute severe asthma (see Chapter 21) involves understanding asthma, knowing the patient, instituting stepwise but effective therapy, establishing a physician–patient relationship, and emphasizing early therapy for increasingly severe asthma.

Personal peak flow monitoring will not help the unreliable, noncompliant patient. A personal peak flow monitor possibly will improve asthma if it can formalize antiasthma therapy in the otherwise noncompliant patient.

Some patients with very severe asthma will have steroid-resistant asthma, defined by a <12% increase in FEV_1 after 1 to 2 weeks of prednisone administered as 20 mg twice daily. Steroid-sensitive patients have a >15% increase in FEV_1. The best treatments for steroid-resistant patients are under investigation, but continued moderate to high dosages of prednisone on a daily basis may cause more side effects than therapeutic benefit.

Treatment of the Acute Attack of Asthma

In mild attacks, the use of inhaled (or oral depending on age) short-acting β_2-adrenergic agonists every 4 to 6 hours may suffice. Inhaled β_2-adrenergic agonists can be administered by MDI β_2-adrenergic with or without a spacer device, depending on patient technique, or by nebulizer. Patients must be advised about their proper use and warned against overuse. Alternatively, in patients with persistent mild asthma, as-needed ICS may be sufficient therapy.

In patients with persistent moderate and severe asthma, it is necessary to continue the currently prescribed ICS and add a β_2-adrenergic agonist or, depending on the severity of the attack and the ease of control of the patient's asthma, and add a short course of oral corticosteroid (e.g., prednisone, 1 to 2 mg/kg for children and 40 to 60 mg for adults). When signs and symptoms of asthma are refractory to 2 to 3 treatments with inhaled short-acting β_2-adrenergic agonists or nebulized albuterol, acute severe asthma exists, a medical emergency requiring corticosteroids and intensified monitoring. Its treatment is presented in Chapter 21 and Table 19.12. For patients who are not that ill acutely and can initiate therapy at home, doubling of the dosage of ICS from a therapeutic, controlling dosage has not been found to be effective if the patient already is using a reasonable dosage. It may be possible to quadruple the ICS dose and achieve control of the acute attack, but this issue remains underinvestigation as one study failed to meet the primary outcome (239).

Because tachyphylaxis to short-acting β_2-adrenergic agonists has been demonstrated *in vivo* and *in vitro* in some studies, concern has been expressed that prior administration of β_2-adrenergic agonists may abrogate clinical response from current emergency treatment of asthma. Failure of a patient to improve suggests increasingly severe asthma (bronchoconstriction, hyperinflation, mucus plugging of airways, etc.), not tachyphylaxis to short-acting β_2-adrenergic agonists. In patients using salmeterol regularly but for whom emergency department care for asthma was required, nebulized albuterol at 2.5 or 5.0 mg produced similar improvement in PEFR, compared with patients who had not been using salmeterol. The responses to albuterol were not impaired.

There may be a modest benefit of combining ipratropium bromide with nebulized albuterol (3,4). Although ipratropium bromide is safe, its bronchodilating effect is small.

Treatment of Persistent Asthma

The management of persistent asthma entails a continuous broad control that should be tailored to each patient. Features of general management, as discussed previously, must be included in the treatment regimen. Significant allergic factors are treated by environmental control combined with appropriately administered allergen immunotherapy. Immunomodulator treatments should be considered for persistent moderate and severe asthma in patients (Table 19.6). In each patient, secondary contributing factors or comorbidities should be evaluated

and controlled as best as possible. Some of these factors include cessation of smoking or illicit drug use, adherence with medications, effective inhaler technique, and treatment of concurrent medical conditions, such as allergic rhinitis or rhinosinusitis, GERD (SERD or NERD), COPD, and CHF. Medication intolerance and variations in responses to pharmacotherapy should be identified.

Patients with persistent asthma require anti-inflammatory therapy (preferably ICS, but cromolyn, leukotriene receptor antagonists or inhibitors, and theophylline are acceptable controller medications in some situations (Table 19.6) (3,4). In patients with intermittent asthma, inhaled short-acting β_2-adrenergic agonists taken only when or before symptoms occur may suffice. A patient who has asthma only with upper respiratory infections should be instructed to begin either an ICS or ICS/β_2-adrenergic agonist at the first sign of coryza. For some patients, serial monitoring of PEFRs or physician examination of sputum for eosinophils may be useful. Children or some adults, who wheeze only with upper respiratory infections, may need to use ICS (or ICS/β_2-adrenergic agonist combination) as scheduled therapy because of the persistence of silent pulmonary function abnormalities and airway inflammation. This point needs to be explained clearly to obtain sufficient control of asthma. At a minimum, patients with persistent moderate or severe asthma clearly require scheduled daily ICS (3,4) used properly (with or without a spacer device). An action plan for regular or intensified therapy is indicated, especially for times when symptoms are not controlled by ongoing medications.

TABLE 19.11 CLINICAL AND ANTI-INFLAMMATORY EFFECTS OF CORTICOSTEROIDS IN ASTHMA

- Reduction of symptoms (cough, wheezing, dyspnea) from asthma
- Improvement in morning expiratory flow rates and intraday variation
- Reduces need for β_2-adrenergic agonists in persistent asthma
- Increases the β_2-adrenergic receptor density
- Can prevent deterioration leading to acute severe asthma (status asthmaticus)
- Improves oxygenation and time to discharge after acute severe asthma (status asthmaticus)
- Reduces recidivism readmission to emergency department after acute therapy
- Decreases mucus production and sputum eosinophilia

- Reduction of fraction of expired NO

- Regeneration of bronchial epithelium

- Increases the ratio of ciliated columnar cells to goblet cells in the bronchial epithelium

- Causes a modest lessening of nonspecific bronchial hypersensitivity

- Increases numbers of intraepithelial nerves

- Partial inhibition of the late bronchoconstrictive responses to aerosol allergen provocation after one dose of inhaled corticosteroid

- Partial inhibition of the early and late bronchoconstrictive responses to aerosol allergen provocation after 4 d of inhaled corticosteroids and early response after 1 wk of prednisone

- Reduction in recovery of eosinophils and mast cells in bronchoalveolar lavage

- Reduction of eosinophils, mast cells in the respiratory epithelium and lamina propria

- Reduction of production of superoxide anions by eosinophils

- Reduction of numbers of activated lymphocytes in bronchoalveolar lavage and mucosa

- Reduction of $ex\ vivo$ bronchoalveolar (macrophage) cell synthesis of leukotriene B_4 and thromboxane B_2

- Reduction in bronchoalveolar lavage cells expressing mRNA for interleukin-4 (IL-4) and IL-5 with an increase in interferon-γ–positive cells

- Activation of the glucocorticoid receptor in the cytoplasm causing translocation into the nucleus

- Reduces histone acetyltransferase activity which reduces unwinding of chromatin (DNA-histone) and transcription

- Increases histone deacetylation causing transcriptional repression of inflammatory gene expression

- Increases FOXP3 mRNA expression in $CD4^+CD25^+T_{reg}$ cells

- Reduction in the stability of mRNA transcripts

If the patient has prednisone-dependent asthma with nocturnal symptoms, effective control of these symptoms may be achieved either by increasing the morning prednisone dose or by increasing the use of ICS. Because of the trade-off between severe allergic asthma from a pet and incomplete control of asthma with polypharmacy, it is advisable to revisit the recommendation for removal of the pet.

A patient being treated with scheduled, noncorticosteroid therapy using β_2-adrenergic agonists, leukotriene modifier, theophylline, ipratropium bromide,

tiotropium, or a combination of these agents may have an exacerbation of asthma. For these patients, additional β_2-adrenergic agonists may result in side effects. Additional theophylline may result in toxicity without clinical improvement. Short-term oral corticosteroid or perhaps ICS therapy or both, is the most appropriate therapy. If longer use of oral corticosteroids or more frequent courses are required, ICS/β_2-adrenergic agonist combination therapy or high-dosage inhaled-corticosteroid steroid and alternate-day prednisone should be considered after the patient has improved (Table 19.11). Such patients should undergo allergy–immunology consultation and receive appropriate anti-inflammatory medications.

When persistent asthma is not controlled effectively with ICS or an ICS/β_2-adrenergic agonist combination, other medications may be tried. Cromolyn, leukotriene receptor antagonists or biosynthesis inhibitors, theophylline, tiotropium, or a combination of these should be tried in some patients. Cromolyn can be used prophylactically for intermittent but unavoidable animal exposure. However, if added to scheduled ICS therapy, the additional benefit of cromolyn may or may not occur. However, a 1- to 2-month trial of cromolyn or leukotriene receptor antagonist or biosynthesis inhibitor should be attempted (see Chapter 36).

Because of their frequent recurrence, it is generally advisable that surgical removal of nasal polyps be considered only after local corticosteroid aerosol treatment, coupled with good medical and allergy–immunology management, have not been effective in decreasing obstruction and repeated infections. Sinus surgery should also be considered when more conservative treatment (medical and allergic-immunologic) has resulted in little or no success in preventing recurrent sinusitis. Some patients with recurrent exacerbations of CRS have common variable immunodeficiency or specific antibody deficiency (see Chapter 4). Referral for surgery typically occurs when patients have four episodes of rhinosinusitis per year, asthma episodes repeatedly triggered by acute rhinosinusitis, CRS resistant to medical therapy, and in patients in whom allergic fungal rhinosinusitis is suspected (see Chapter 12).

Anxiety or depression or other psychologic or psychiatric conditions may aggravate asthma. When these conditions are present, antidepressants may be necessary. Psychologic or psychiatric evaluation should be obtained. Often, it has been assumed by the lay public as well as by some members of the medical profession that asthma is primarily an expression of an underlying psychologic disturbance. This attitude has inappropriately prevented proper medical and

allergy-immunologic management in some patients. In most patients, psychiatric factors are of little to no significance in the *cause* of the disease. Nevertheless, psychologic factors may be a contributory aggravating factor for asthma. Asthma is a chronic disease that may also be associated with significant impairment of physical and social activity. These factors in themselves may lead to the development of psychologic dysfunction with reduced quality of life. Often, when symptoms of asthma are brought under control, concomitant improvement of psychologic dynamics occurs. When schizophrenia and corticosteroid-dependent asthma coexist, the physician may become frustrated because of the patient's prednisone phobia, medication or appointment nonaderence, and abuse of emergency medical facilities. Depot methylprednisolone or triamcinolone may be beneficial or lifesaving in patients if they keep their medical appointments.

The decision to use a peak flow meter should be kept in perspective. In adherent patients, measurements can be an early warning system that leads to implementation of the action plan. If the patient is under effective control of asthma such that exercise tolerance is satisfactory, nocturnal wheezing is absent or infrequent, emergency department visits are not happening, and symptoms of asthma are uncommon or mild, little benefit from a peak flow meter will occur. If the peak flow meter can help emphasize patient adherence with antiasthma measures and medication, its addition to a regimen will be valuable. Some patients submit peak flow diaries consistent with their expectations or perceptions of asthma. Other patients do not contact their physicians or intensify therapy for peak flow rates of 30% of predicted, nullifying any value to the patient or physician. There may be discrepancies between measurements of PEFR and FEV_1, resulting in overestimation or underestimation of the FEV_1.

Treatment of Intractable, Difficult to Treat, or Refractory Asthma

Intractable asthma refers to persistent, incapacitating symptoms that have become unresponsive to the usual therapy, including moderate to large doses of oral corticosteroids and high-dose ICS. These cases fortunately are few. Their constant medical and nonmedical requirements are heavy social and financial burdens on their families. Further, these patients may have cushingoid features from daily prednisone use. Most patients with intractable asthma are not deficient in antiproteases. Some will meet criteria for steroid-resistant asthma. Their asthma may represent an intense inflammatory process with marked

bronchial mucosal edema, mucus plugging of airway, and decreased lung compliance and more easily collapsible airways. In cases of intractable asthma, a home visit may be beneficial for the patient as well as for the physician or other health care provider. For example, the finding that an animal resides in the home of a patient with intractable asthma may explain the apparent failure of oral and high-dosage ICS to improve the control of asthma. Also, when speaking to the patient by telephone, a physician's overhearing of a barking dog may provide the explanation for the difficulty controlling the asthma. Thus, intractable asthma is not always intractable.

Some cases of intractable asthma include those patients with severe, corticosteroid-dependent asthma in whom adequate doses of corticosteroids have not been used, either by physician or patient avoidance. After initiation of appropriate doses of prednisone and clearing of asthma, many cases can be controlled with alternate-day prednisone and ICS or with ICS/β_2-adrenergic agonist alone. Leukotriene receptor antagonists or biosynthesis inhibitors should be tried. Other patients require moderate to even high doses of daily prednisone for functional control. Fortunately, this latter group is small. Occasionally, it includes patients with severe lung damage from ABPA or with irreversible asthma (149). Other patients may have asthma and COPD, with most of their disease being COPD. Pharmacologic improvement of asthma can be achieved, but the irreversible obstructive component cannot be altered significantly. Still other patients have VCD without concomitant obstruction of expiratory flow.

In an attempt to reduce the prednisone dosage in patients with intractable asthma (severe corticosteroid–dependent asthma), some physicians have recommended using methylprednisolone (Medrol) and the macrolide antibiotic, troleandomycin, in an effort to decrease the prednisone requirement. Although prednisone dosage can be reduced, the decreased clearance of methylprednisolone by the effect of troleandomycin on the liver still may result in cushingoid obesity or corticosteroid side effects, at times exceeding prednisone alone. Therefore, methylprednisolone and troleandomycin are reduced as the patient improves. This approach has little to offer. The antifungal drug itraconazole also decreases metabolism of methylprednisolone. It remains unclear if empiric use of clarithromycin has any role in management of intractable or very severe asthma.

High doses of intramuscular triamcinolone have been recommended and are effective therapy. However, they were associated with expected adverse effects, such as cushingoid facies, acne, hyperglycemia, hirsutism, and myalgias. In

patients with severe asthma who were receiving high dosage of beclomethasone dipropionate and oral corticosteroids but still had elevated eosinophils in sputum, intramuscular triamcinolone resulted in reduced sputum eosinophils and increased FEV_1. These findings questioned the notion that patients with severe asthma and sputum eosinophilia, despite oral and ICS treatment, actually are refractory to corticosteroids.

In adults, methotrexate (15 mg/week) was reported to be steroid sparing in a group of patients whose daily prednisone dosage was reduced by 36.5% (351). A double-blind placebo-controlled trial over a shorter period, 13 weeks, did not confirm a benefit of methotrexate, in that both methotrexate and placebo-treated patients had prednisone reductions of about 40% (352). Such a finding is consistent with the Hawthorne effect, improvement that occurs simply as a result of participant observation; in other words, entry into a study itself can have a beneficial effect. The use of methotrexate (and drugs like azathioprine) remains experimental and unproved for treatment of persistent severe asthma. Methotrexate was not recommended for administration in severe asthma by an international expert group as of 2016 (353).

Cyclosporine has also been disappointing and appears to provide only prednisone-sparing effects that are not sustainable after cyclosporine is discontinued (354). The administration of gold therapy for asthma has been described but is associated with recognized toxicity (355).

It is possible to reduce the elevated levels of tumor necrosis factor-α (TNFα) in sputum from patients with severe asthma and TNFα participates in airway hyperreactivity (356). This observation suggests that antagonizing TNFα might be of benefit in treatment of asthma (357). In patients with persistent moderate asthma, infliximab, a recombinant antibody to soluble TNFα reduced PEFR variability, reduced number of exacerbations and delayed time until exacerbation (357). The role of anti-TNFα therapy in severe or intractable asthma remains a possibility for future study. Omalizumab, mepolizumab, reslizumab, and other recombinant antibodies (not yet approved by the FDA) can provide benefits in persistent severe asthma, but it remains to be established how effective these antibodies will be for difficult to treat asthma.

Studies with dapsone, hydroxychloroquine, and intravenous gammaglobulin (358,359) are not convincing in the management of difficult cases of asthma. Nebulized lidocaine (40 to 160 mg, four times daily) has been investigated in adults (360) and children (361). Its role remains to be established, but lidocaine is known to shorten the survival of eosinophils. Patient must be informed not to

eat or drink for 1 hour after treatments because of reduced gag and cough reflexes. In steroid-dependent patients, a confounding factor is unrecognized respiratory or skeletal muscle weakness. Although this finding may result from use of intravenous corticosteroids and muscle relaxants, it can have residual effects. Every attempt must be made to reduce the prednisone dose and eventually to use alternate-day prednisone if possible. Furthermore, very high dosages of ICS such as >2,000 µg/day may cause adrenal suppression or adverse effects on bone health and still not improve asthma.

Another approach for moderate and severe asthma is bronchial thermoplasty. It is hoped that there will be tangible clinical benefit from the reduction in the smooth muscle mass.

Asthma is a long-term condition with fluctuations. In a study of the natural history of severe persistent asthma in patients who required at least 1 year of prednisone in addition to other pharmacotherapy (β_2-adrenergic agonists, theophylline, and high-dose ICS), avoidance measures, and possibly immunotherapy, prednisone-free intervals occurred, even lasting several years, before prednisone was required again (362). It was uncommon to have greater prednisone requirements, although usually, in these cases of persistent severe asthma, prednisone dosages were stable over time, or reductions occurred. The conclusion is that in assessment of novel treatments for persistent moderate, severe, or refractory asthma, adequate "wash-in" periods are needed in studies of such patients; otherwise, credit may be given to a new therapy inappropriately.

The term *glucocorticoid-resistant* has been applied to patients with asthma who do not increase their FEV_1 by 12% after 1 week administration of prednisone 40 mg daily (363). Experimentally, glucocorticoid receptor downregulation on T lymphocytes has been identified, suggesting that such patients could have impaired *inhibition* of activated T lymphocytes in asthma. For example, in cells from corticosteroid-resistant patients, dexamethasone *in vitro* did not *inhibit* T-lymphocyte proliferation to the mitogen phytohemagglutinin. Incubation with vitamin D also produced little effect in monocytes from patients with steroid resistant as opposed to steroid-sensitive patients (363). Excessive and harmful allergic inflammation characterizes this form of difficult to treat asthma.

In summarizing the discussion of intractable or difficult to treat or refractory asthma, it is worth reconsidering the differential diagnosis of asthma. Some patients will have unrecognized VCD and asthma. Other patients may misrepresent their dosages and use of prednisone.

ACUTE SEVERE ASTHMA (STATUS ASTHMATICUS)

Acute severe asthma (status asthmaticus) is defined as severe asthma unresponsive to emergency therapy with β_2-adrenergic agonists (see Chapter 21). It is a medical emergency for which immediate recognition and treatment are necessary to avoid a fatal outcome. For practical purposes, acute severe asthma is present in the absence of meaningful response to two aerosol treatments with β_2-adrenergic agonists or 1 hour of nebulized albuterol.

A number of factors have been shown to be important in inducing acute severe asthma and contributing to the mortality of asthma. About half of patients have an associated respiratory tract infection. Some have overused short-acting β_2-adrenergic agonists before developing refractoriness. In the aspirin-exacerbated respiratory disease asthmatic patient, ingestion of aspirin or related cyclooxygenase-1 inhibitors may precipitate acute severe asthma. Exposure to animal dander (especially cat dander) in the highly atopic patient may contribute to development of acute severe asthma, particularly when this is associated with an upper respiratory infection. Withdrawal or too sudden reduction of oral or ICS may be associated with the development of acute severe asthma. In many situations, both the patient and physician or health care provider are unaware of the severity of progression of symptoms, and often earlier and more aggressive medical management would have prevented the need for emergency department visit or hospitalization. The inappropriate use of soporific medications in the treatment of acute severe asthma has contributed to the development of respiratory failure.

Acute severe asthma requires immediate treatment with high-dose corticosteroids either parenterally or orally. Patients with acute severe asthma must be hospitalized where close observation and ancillary treatment by experienced personnel are available. If respiratory failure occurs, optimal treatment often involves the combined efforts of the emergency department physician, pulmonary disease critical care specialist, and/or anesthesiologist.

Initial laboratory studies should include a complete blood count, Gram stain with culture and sensitivity of the sputum, chest radiograph, serum electrolytes, and chemistries; pulse oximetry; and perhaps arterial blood gas studies (Tables 19.12 and 19.13). There may be considerable improvement during treatment of acute severe asthma without improvement in PEFR, FEV_1, or FVC. This apparent lack of spirometric improvement occurs even though the hyperinflation

of lung volumes is diminishing in association with a reduction in the elastic work of breathing.

The severity of acute asthma is organized into four stages (Table 19.13). Stage I signifies the presence of airway obstruction only. Because of the associated hyperventilation, the PCO_2 is low, and the pH is, therefore, slightly alkalotic (respiratory alkalosis). The PO_2 in stage I is normal. Spirometric study shows only a decrease in FEV_1, with a normal vital capacity. As symptoms progress, obstruction of the airway increases, compliance decreases, and air trapping and hyperinflation develop. As a result of the latter changes, the FRC increases, and the vital capacity is decreased. In stage II, V/Q imbalance with hypoxemia occurs. These changes, however, are not enough to impair net alveolar ventilation; thus, although PO_2 is lowered, PCO_2 remains low, and an alkalotic pH persists. With progressive severity, net alveolar ventilation decreases, and a transitional period exists (stage III), in which the PCO_2 increases and the pH decreases, so that now both values appear to be normal. When the blood gas study shows hypoxemia in the presence of a normal PCO_2 and pH, close supervision and frequent determinations of pH and PCO_2 are essential to evaluate the adequacy of treatment and the possible progression to respiratory failure characterized by hypoxemia and elevated PCO_2 (stage IV). Clinical observation alone is inadequate in determining the seriousness of acute severe asthma.

TABLE 19.12 INITIAL TREATMENT OF ACUTE SEVERE ASTHMA

1. Corticosteroid therapy (give immediately in the office or emergency department). Methylprednisolone (Solu-Medrol), 0.5–1.0 mg/kg intravenously every 6 h; or hydrocortisone (Solu-Cortef), 4 mg/kg intravenously every 6 h; or prednisone, 1 mg/kg orally every 6 h (minimum is 80 mg methylprednisolone equivalent/24 h)

2. β-Adrenergic agonists

   Choice of approaches available:

   a. Aerosolized therapy; albuterol or levalbuterol

      Repeat twice at 20-min intervals, then at reduced frequency. May use continuous nebulization of albuterol or levalbuterol.

   b. Epinephrine, 0.01 mL/kg of 1:1,000 solution, intramuscularly not to exceed 0.3–0.4 mL in adults. May repeat twice at 20-min intervals, then at reduced frequency.

   c. If a patient does not respond to (a), try (b).

3. Ipratropium bromide (can be combined with albuterol)

4. Hospitalize

5. Laboratory studies

    White blood cell count with differential

    Chest radiograph

    Pulse oximetry or arterial blood gas

    Serum electrolytes and chemistries

    Sputum Gram stain, culture, and sensitivities (some cases)

    Bedside spirometer may be useful, but not essential

    Electrocardiogram (some cases)

6. Oxygen therapy; 2–3 L/minute nasal cannula (best guided by arterial blood gas determination)

7. Correct dehydration

8. Aminophylline therapy (controversial because of unclear benefit for many patients). Check theophylline concentration if chronic therapy. Administration is discouraged because efficacy has been questioned during emergency use.

9. Antibiotic therapy. When indicated for bronchitis or exacerbations of rhinosinusitis.

10. Impending or acute respiratory failure. Repeat β_2-adrenergic agonists; endotracheal intubation with assisted or controlled ventilation.

TABLE 19.13 SPIROMETRY AND BLOOD GASES IN ASTHMA AS RELATED TO THE STAGE OR SEVERITY

	FEV1	VITAL CAPACITY	Po$_2$ (NORMAL, 90–100 mm Hg)	Pco$_2$ (NORMAL, 35–40 mm Hg)	pH (NORMAL, 7.35–7.43 mm Hg)
Stage I (respiratory alkalosis)	↓	Normal	Normal	↓	>7.43
Stage II (respiratory alkalosis)	↓↓	↓	↓	↓↓	>7.43
Stage III	↓↓↓	↓↓	↓↓	35–40	7.35–7.43

| Stage IV (respiratory acidosis) | ↓↓↓↓ | ↓↓↓ | ↓↓↓ | ↑↑↑ | <7.35 |

FEV$_1$, forced expiratory volume in 1 second; ↑, increased; ↓, reduced.

Patients who experience a single episode of acute severe asthma can be at increased risk of future episodes of acute severe asthma or fatalities from asthma. It is important to consider what factors contributed to the acute episode and what approaches may be taken to prevent future emergency department visits, hospitalizations, or fatality from asthma. A virtual "discharge conference," performed during the allergy–immunology or asthma specialist consultation, for example, should focus on prevention of future episodes requiring emergency treatment.

Treatment

Although many patients with acute severe asthma manifest signs of restlessness and anxiety, the use of anxiolytic drugs is contraindicated. The inability to achieve adequate ventilation may cause the patient to appear excessively anxious. Such patients likely are in stage III or IV (Table 19.13) and may require emergent intubation. Some patients in acute severe asthma are dehydrated. The hyperventilation and increased work of breathing cause water loss through the lungs and skin.

In patients with a compromised cardiovascular system, sodium and water overload must be avoided. Because a high dose of parenteral corticosteroids is used in these patients, adequate potassium supplementation must be included in the intravenous therapy. In some adults, 80 mEq of potassium chloride per 24 hours (not to exceed 20 mEq/hour) is indicated. Frequent serum electrolyte determinations provide the best guide for continued electrolyte therapy. High dosages of albuterol can result in modest reductions in serum potassium and magnesium.

It is no longer considered that aminophylline should be administered. However, if it is used, aminophylline should be given intravenously using constant infusion and being cognizant of serum theophylline concentrations and drug interactions.

Because nearly all patients are hypoxemic, oxygen therapy is required. Ideally, blood gas determinations should guide proper therapy. Therapeutically, a

PO_2 of 60 mm Hg or slightly higher is sufficient. This often can be accomplished with low flow rates of 2 to 3 L/minute by nasal cannula. Ventimasks calibrated to deliver 24%, 28%, and 35% oxygen may also be used. The necessity for higher concentration of oxygen to maintain a PO_2 of 60 mm Hg usually signifies the presence of thick tracheobronchial secretions and of V/Q mismatch. Also, β_2-adrenergic agonists initially may cause a mild decrease in PO_2 by increasing pulmonary blood flow to poorly ventilated alveoli, thus increasing V/Q mismatch. Oxygen helps protect against this effect. It is cautioned that, in patients with asthma complicated by COPD, chronic hypercapnia may be present, and hypoxemia remains the only respiratory stimulus. Oxygen therapy during an acute respiratory insult in these patients may enhance progression to respiratory failure. Close clinical observation and frequent blood gas monitoring are important in preventing this complication.

With evidence of infection (i.e., purulent sputum containing polymorphonuclear leukocytes, fever, acute rhinosinusitis, or radiographic evidence of pneumonia), antibiotics should be administered. In some instances, infection may be present in the absence of these suggestive findings; conversely, eosinophils may result in sputum that appears purulent but contains no bacteria or neutrophils. Thus, antibiotics should not be prescribed routinely. Results of sputum culture should dictate change in antibiotic therapy. If rhinosinusitis is present, other antibiotics, such as amoxicillin-clavulanate, azithromycin, clarithromycin, or trimethoprim-sulfamethoxazole, can be administered.

Large doses of corticosteroids are essential immediately in acute severe asthma with a minimum of 80 mg/day of methylprednisolone in adolescents and adults (240). With improvement, oral doses of prednisone can be substituted at 60 to 80 mg/day in an adult and 2 mg/kg/day in children. There is no additional benefit of 1,000-mg doses/day of methylprednisolone. It is possible to manage acute severe asthma without giving intravenous corticosteroids. For example, when prednisone, 2 mg/kg twice daily, was compared in children with methylprednisolone, 1 mg/kg four times daily given intravenously, equal efficacy was found for hospital length of stay and respiratory parameters (364). For adults, prednisone, 60 mg immediately and every 6 hours, can be administered. Chemistries, including glucose and potassium, should be determined. Magnesium rarely can be decreased in ambulatory patients and may contribute to respiratory muscle dysfunction but should be considered in some situations, especially after mechanical ventilation.

For acute dyspnea, nebulized or aerosolized β_2-adrenergic agonists may be

administered every 4 hours or continuously (a treatment that does not produce superior results); however, little or no effect may be seen in the first 24 hours. Treatment of acute severe asthma is summarized in Tables 19.8, 19.12, 19.13, and Chapter 21. There remains no defined role for magnesium (unless the patient has hypomagnesemia) or heliox.

■ RESPIRATORY FAILURE

Most patients with acute severe asthma respond favorably to the management described previously and in Chapter 21. In those patients who continue to deteriorate, other aggressive measures must be included to prevent respiratory failure, which may be defined as a PCO_2 of greater than 50 mm Hg or a PO_2 of less than 50 mm Hg. The important features of treatment at this stage include measures to maintain adequate alveolar ventilation and to protect from the severe acid–base disturbances that may arise.

Signs of impending respiratory failure result from the combined effects of hypercapnia, hypoxia, and acidosis. Clinically, because of fatigue, inability to talk, and exhaustion, thoracic excursion is decreased, and auscultation of the chest may show decreased respiratory sounds because there is a decrease in air flow. Because of accompanying stupor, the patient may appear to be struggling less to breathe. These two features may give a false impression of improvement. Signs and symptoms of hypoxia include restlessness, confusion or delirium, and central cyanosis, which is present when arterial saturation is less than 70% and arterial PO_2 is less than 40 mm Hg. Hypercapnia is associated with headache or dizziness, confusion, unconsciousness, asterixis, miosis, papilledema, hypertension, and diaphoresis. Other danger signs in the patient with acute severe asthma include the presence of pulsus paradoxus, marked inspiratory retractions, inability to speak in full sentences, and cardiac arrhythmias that may lead to cardiac arrest. It has been suggested that retractions are equivalent to pulsus paradoxus and certainly easier to detect.

Acute chest pain is consistent with myocardial ischemia or infarction, pulmonary infarction (emboli usually cause dyspnea without chest wall pain), or rib fractures. When subcutaneous emphysema is present, chest pain suggests pneumomediastinum or pneumothorax. Acidosis and hypoxemia contribute to pulmonary vasoconstriction, with resultant pulmonary hypertension and right ventricular strain. The acidosis is primarily respiratory in origin, but with severe hypoxemia, aerobic metabolism is impaired, and there is an accumulation of pyruvic and lactic acid (end products of anaerobic metabolism). These result in a

superimposed metabolic acidosis. The presence of these signs and symptoms associated with development of acidosis and hypercapnia usually demands the institution of mechanical ventilation.

Patients who survive an episode of acute severe asthma who have required mechanical ventilation should be considered to have potentially (near) fatal asthma (92,152,154). Attempts should be made to identify reasons for the episode of acute severe asthma. Some examples include allergic asthma from animal exposure, such as cats, dogs, gerbils, or hamsters; molds (fungi); upper respiratory infections; acute rhinosinusitis; nonadherence with outpatient advice; undertreatment on an ambulatory basis (failure to receive a short course of prednisone when the deterioration began); use of aspirin or cyclooxygenase-1 inhibitor within 3 hours of onset of severe asthma symptoms; or substance abuse, such as cocaine or heroin use (114,365,366). Some patients have unanticipated severe attacks, but these patients should undergo allergy–immunology or asthma specialist evaluation and receive more intensive pharmacotherapy. Acute respiratory failure may occur seemingly without apparent explanation and can be fatal. Furthermore, not all patients with acute respiratory failure report moderate-to-severe persistent symptoms of asthma. However, some of these patients are poor perceivers of dyspnea with decreases in FEV_1, yet are not recognized as having more than mild (persistent) symptoms.

PREPARATION OF THE ASTHMATIC PATIENT FOR SURGERY

For elective surgery, the patient with asthma ideally should be evaluated 1 to 3 weeks in advance as an ambulatory patient so that adequate treatment can be instituted to ensure optimal bronchopulmonary status. If the patient is a corticosteroid dependent with asthma, increase the dose of prednisone instead of relying on increased use of β_2-adrenergic agonists or ICS to ensure complete control of asthma. If the patient is receiving scheduled ICS, a short course (4 to 5 days) of prednisone (20 to 40 mg/day) before surgery is recommended to maximize pulmonary function (367). Pulmonary function testing should be obtained, at least FVC and FEV_1. The main need for oral corticosteroids, however, is prevention of intraoperative or postoperative asthma rather than adrenal crisis.

Hydrocortisone, 100 mg intravenously, should be started before surgery and continued every 8 hours until the patient can tolerate oral or inhaled medications (367,368). Often, just one dose of hydrocortisone is necessary. If no

postoperative asthma occurs, the hydrocortisone dose can be discontinued. The doses of prednisone and hydrocortisone needed to control asthma do not increase postoperative complications, such as wound infection or dehiscence (367,368).

In patients with asthma, optimal respiratory status should be achieved before surgery occurs. The cold temperature in the preoperative anesthesia rooms may precipitate acute asthma. Manipulation of the upper airway (e.g., suction, oropharyngeal airway) may cause bronchoconstriction during conscious sedation or anesthesia.

After surgery, the patient should be evaluated carefully. β_2-Adrenergic agonists, deep-breathing exercises, adequate hydration, and gentle coughing should be instituted to avoid accumulation of secretions and atelectasis. Use of epidural or spinal anesthesia is not necessarily safer than general anesthesia.

COMPLICATIONS OF ASTHMA

Although they are rare, pneumothorax, pneumomediastinum, and subcutaneous emphysema can occur during an attack of severe asthma. These complications are thought to result from the rupture of overdistended peripheral alveoli. The escaping air then follows and dissects through bronchovascular sheaths of the lung parenchyma. Often, the amount of air is minimal, and no chest tube insertion is required. When severe tension symptoms occur, insertion of a chest tube under a water seal for pneumothorax may be needed. Tracheostomy may be required for severe tension complications of pneumomediastinum. A common feature of these conditions is chest pain; this is not expected with uncomplicated asthma, and when present should suggest the possibility of the extravasation of air. On auscultation of the heart, a crunching sound synchronous with the heartbeat may be present in a patient with pneumomediastinum (Hamman sign).

Minimal areas of atelectasis may occur in asthma. Atelectasis of the middle lobe is a common complication of asthma in children. It is often reversible with prednisone or parenteral corticosteroids and β_2-adrenergic agonists. It results from mucus plugging and edema of the middle lobe bronchus. When the atelectasis does not respond to the above treatment within a few days, bronchoscopy is indicated for both therapeutic and diagnostic reasons. Occasionally, children may develop atelectasis of other lobes or of an entire lung. ABPA (see Chapter 24) and cystic fibrosis must be excluded in these patients, as in any patient with asthma.

Rib fracture and costochondritis may occur as a result of coughing during

attacks of asthma. In a few patients, severe coughing from asthma may result in cough syncope. In women, severe coughing results in urinary incontinence. Men or women may experience fecal incontinence in rare cases.

Chronic bronchitis and centrilobular emphysema are not complications of asthma. These conditions occur with irreversible destruction of lung tissue, whereas asthma is at least a partially to completely reversible inflammatory condition. In some patients, asthma and emphysema or chronic bronchitis may coexist. The identification of bronchiectasis in a patient with asthma should raise the possibility of ABPA, undiagnosed cystic fibrosis, or common variable immunodeficiency or specific antibody deficiency. Hypoxemia from uncontrolled asthma has been associated with adverse effects on other organs, such as myocardial ischemia or infarction.

As stated earlier, there can be excessive loss of FEV_1 over time in adult patients with asthma or reduced lung growth in childhood with or without additional loss of FEV_1 in adolescence or early adulthood (148). Some patients have $FEV_1/FVC < 70\%$ in the third decade of life (148). Some adults with long-term asthma, typically with onset in childhood, can be classified as having "irreversible asthma" (149). These patients do not have COPD, ABPA, cystic fibrosis, occupational asthma, or other lung disease, and α_1-antitrypsin concentrations are not reduced. High-resolution CT scanning of the lungs does not demonstrate fibrosis or other explanations. Most of these patients do not have steroid-resistant asthma because they have more than 12% bronchodilator response to 1 (or 2) weeks of daily prednisone. However, their ultimate FEV_1 after prednisone and other pharmacotherapy is markedly impaired, with a mean FEV_1 percentage of 57 (149).

Treatment of asthma can help avoid the excessive loss of FEV_1 and preserve lung function (369–371) in patients with mild-to-severe asthma. For example, in a study over a period of 10 years in adults, the group of nonsmokers receiving ICS therapy had an annualized loss of FEV_1 of 22.8 mL/year compared with 46.1 mL/year in those patients who did not use ICS (369). There are advantages of initiating ICS therapy within the first 2 years of the diagnosis of asthma (370). In children, loss of lung function occurs in the first 3 years of life and can persist (148,160,371). In a study of 16-year-old adolescents who had been evaluated since birth, when there was a history of transient wheezing with lower respiratory tract infections in the first 3 years of life or persistent wheezing (wheezing before age 3 years and wheezing at age 6 years), there was a loss of

FEV$_1$ of 75 and 87 mL, respectively, compared with 23 mL in late-onset wheeze patients (wheeze by age 6 years but not earlier) (160). These data support the finding that transient wheezers and persistent wheezers by age 6 years *already* have reductions in lung function that persist, whereas the onset of asthma from ages 6 years and greater did not result in excessive loss of FEV$_1$ by age 16 (160).

Complications of treatment of asthma include adverse effects from treatments such as from ICS and oral corticosteroids, such as the possibility of bone loss (osteopenia), osteoporosis, or even fracture. Complications of long-acting β$_2$-adrenergic agonists have been a source of dispute, but their benefits when combined with an ICS are far greater than risks.

MORTALITY

Death from asthma commonly occurs either as a result of acute severe asthma progressing to respiratory failure or suddenly and unexpectedly from severe bronchoconstriction and hypoxia, perhaps with a terminal cardiac arrhythmia or mucus plugging leading to asphyxiation. The increase in mortality rate from asthma that occurred in the 1980s in the United States appeared to stabilize by 1996 and peaked at over 5,000 cases/year before declining to 4,055 cases as of 2003 and 3,651 as of 2014 (95). The use of repeated doses of β$_2$-adrenergic aerosols has been suspected to be a contributing factor in some of these deaths. This interpretation alone is unlikely to be a satisfactory explanation because the quality of care, or lack of it, in the antecedent days (or weeks) before the fatal event is insufficient or misguided. In some cases, the death is seemingly unavoidable.

Undue reliance on inhaled β$_2$-adrenergic agonists by patients and physicians may contribute to fatalities in patients with severe exacerbations of asthma because essential corticosteroid therapy is not being administered. For historic purposes, the surge in deaths in the 1980s in New Zealand associated with the availability of albuterol inhalers without prescription and physician guidance has been considered possibly analogous to the earlier epidemics of the 1960s with potent short-acting β$_2$-adrenergic agonists. In addition, excessive deaths associated with the potent longer-acting β$_2$-adrenergic agonist, femoterol, have been reported. This observation has led to the recommendation that, in persistent asthma, ICS should be used in conjunction with β$_2$-adrenergic agonists.

Some factors that have been implicated in contributing to asthma deaths include the use of sedation in the hospital, illicit drugs and substance abuse

outside the hospital (365,366), the failure to use adequate doses of oral corticosteroids, theophylline toxicity, excessive use of β_2-adrenergic agonists, nonadherence with physician or other health care provider instructions, failure to initiate oral corticosteroids for exacerbations of asthma, and ineffective (lack of aggressive) outpatient management of asthma. One example of the latter phenomenon may be exemplified by the use of ICS or β_2-adrenergic agonists, which will not substitute for oral corticosteroids given acutely as the attack of asthma intensifies. Although there are data supporting the combination product as reliever and maintenance therapy (262–264), it is not certain that this approach will be of value for patients experiencing a severe and potentially fatal episode of asthma. High-risk patients include those who have persistent moderate or severe asthma with frequent episodes of hospitalizations or chronic oral corticosteroid use, chest deformities such as pectus carinatum (pigeon breast), significant wheezing in-between exacerbations of asthma, or gross pulmonary function abnormalities when asymptomatic (poor perceivers) and patients previously requiring mechanical ventilation during respiratory failure, such as those with potentially (near) fatal asthma. After an episode of intubation for asthma, as many as 10% of patients may succumb from their asthma (92,152,154). Because of the reduction in FRC and less ability to apply negative radial traction on bronchi during acute asthma, patients with underlying restrictive lung disease tolerate episodes of acute severe asthma poorly.

FUTURE CONSIDERATIONS

Asthma outcomes will be improved by continued improvements in therapy, implementation of these advances, health care system improvement, and stability of the family and neighborhoods. Specific curative therapy can be realized only when basic pathophysiologic mechanisms are understood. Then, therapeutic modalities can be devised rationally to reverse the underlying pathogenesis.

Many patients with persistent asthma can be managed successfully with an ICS and intermittent but not excessive use of β_2-adrenergic agonists. Additional anti-inflammatory (controller) therapies include cromolyn, nedocromil (if available), LTD_4 antagonists or biosynthesis inhibitors, muscarinic antagonists, and theophylline. None of the medications can substitute for prednisone in patients with oral corticosteroid–dependent asthma. Immunobiologic agents such as omalizumab, reslizumab, and mepolizumab are available in the United States and some other countries. They are not an option in resource poor countries, Unfortunately, ICS are not available in resource poor countries or for some

patients in resource sufficient countries like the United States. Future therapies can be assessed for their ability to (a) decrease symptoms, (b) allow for withdrawal for prednisone or ICS, (c) preserve lung function or limit the loss of FEV_1, and (d) permit improved quality of life without unacceptable adverse effects. Physicians and health care professionals managing patients with asthma should consider allergic triggers in all patients with persistent asthma because about 80% to 90% of patients have IgE antibodies by skin or *in vitro* testing. Subcutaneous allergen vaccine therapy (immunotherapy), especially with trees, grasses, ragweed, and dust mites, remains effective as an immunomodulatory therapy. Some patients respond to injection of molds (fungi). The role of sublingual or other forms of immunotherapy for asthma should be clearer over time. The role of either approach in prevention of asthma remains an important consideration in children with allergic rhinitis.

There is an increasing array of targets in the pulmonary immune system that can be assessed for clinical benefit (see Chapter 38).

Fundamental principles of asthma management include (a) preventing death, disability, and school or work absenteeism/presenteeism, (b) trying to minimize or overcome the effects of airway remodeling and allergic inflammation, mast cell activation, smooth muscle contraction, and pulmonary physiologic abnormalities; and (c) using medications effectively and as safely as possible. It is expected that our treatment modalities will continue to improve and that more specific therapies, whether pharmacologic, allergen immunotherapy, immunologically targeted treatments or other innovative approaches, will be of help to patients. It is hoped that we can take advantage of pharmacogenomic patterns to provide optimal "personalized medicine" for patients with asthma and allergic-immunologic conditions.

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The Infant and Toddler with Asthma

MARY B. HOGAN, SHENIZ MOONIE, AND NEVIN W. WILSON

Recurrent wheezing is a common problem among infants, toddlers, and young children. As a simple starting point, this chapter refers to asthma in children less than 5 years of age with four or more episodes of wheezing. These episodes improve with bronchodilators or anti-inflammatory medications and may or may not be associated with viral infections. In many of these young asthmatics, environmental allergy is already playing an underappreciated role. Scientific advances are slowly being introduced in the identification of asthma in young children. The purpose of this chapter is to review the latest known factors important in the development of asthma in infants and very young children. Also, current difficulties of evaluation and management of wheezing in these children are discussed.

EPIDEMIOLOGY

The prevalence rate for asthma in infants and young children is increasing, particularly in westernized countries. An increase in atopy as well as improvements in disease diagnosis may be contributing factors (1). Children under 3 years of age have a significantly higher risk of being diagnosed with asthma now compared to previous years (2). Hospital admission and emergency department (ED) visit rates are highest among children aged 4 years and under as compared to older asthmatic children (3,4). Asthmatic children under 24 months of age are four times more likely to be admitted to the hospital than teenagers with asthma (5). In Norway, 75% of all children hospitalized for asthma are under 4 years of age (6). Although the number of days in the hospital is declining in older children, hospital length of stay for asthmatic infants is not changing (7). In addition, infants are more likely to require emergency room assistance for asthma exacerbations, and they have higher risk of respiratory failure (8,9). The use of the emergency room for treatment is common among uninsured and

minority infants who present with the highest disease burden, and incur increasing economic direct costs (10). Currently, asthma deaths in all age groups have decreased (11). Overall, it appears that hospitalization rates may be improving for older children, but no substantial progress has been made in improving the quality of life of asthmatic infants (12). The daily quality of life of the very young children with asthma is also diminished because these children have more sleep disruptions, limitations in activity and play than older asthmatic children (4).

NATURAL HISTORY

Wheezing in infants and young children can be divided into three specific phenotypes: early transient wheezers, late-onset nonatopic wheezers, and persistent atopic wheeze/asthma (12). The early transient wheezers have symptoms primarily with viral infections, do not wheeze in between infectious episodes, and are no longer wheezing by the time they are 6 years of age. They often respond poorly to bronchodilators and asthma-controller medications. The late-onset, nonatopic wheezers will wheeze with viral infections and also under other conditions, such as exercise. Their prevalence peaks between 3 and 6 years of age and then gradually declines and frequently becomes asymptomatic early in the second decade of life. The third phenotype combines wheezing with evidence of immunoglobulin E (IgE)-mediated disease. This atopic phenotype is the group most likely to have persistent wheezing. This phenotype gradually increases until it becomes the most common cause of wheezing by 6 years of age.

Most recently, it has been demonstrated that the initial age of asthma diagnosis has been dropping from 4.7 to 2.6 years of age (6). An asthma predictive index (API) (13) was developed to predict infants who were more likely to go on to develop asthma when they were older. It was subsequently modified to include criteria of the child having four or more wheezing episodes with at least one episode being physician diagnosed. In addition, there must be either one major criterion of the following: parental asthma history, physician diagnosed atopic dermatitis or allergic sensitization to at least one aeroallergen, or two minor criteria of allergic sensitization to milk, egg, or peanut, wheezing unrelated to colds and blood eosinophilia $\geq 4\%$ (14). In a subsequent iteration, the University of Cincinnati API (ucAPI) was developed in a cohort of 3-year-old children subsequently diagnosed with asthma at 7 years of age as defined by positive postbronchodilator testing (forced expiratory volume in 1 second increases $\geq 12\%$)/methacholine challenge ($PC_{20} \leq 4$ mg/mL) or by the clinical

need for daily controller therapy (15). Persistent wheezing was defined as physician diagnosed asthma or two or more wheezing episodes in the last 12 months at both 2- and 3-year-old visits. In this study, either persistent wheezing phenotype or a positive ucAPI was associated with meeting criteria of asthma at 7 years of age. Table 20.1 demonstrates the key components of the ucAPI.

Either ucAPI or the modified API (mAPI) are acceptable tools for discerning the appropriateness of a diagnosis of asthma in a wheezing toddler. The strength of the University of Cincinnati study was a focus on slightly different criteria which would readily be usable at the initial consultation visit of a wheezing child. The ucAPI has minor criteria investigable with prick skin testing and without a delay required by a blood draw for the identification of eosinophilia as in the mAPI. In addition, the ucAPI has been linked to asthma at 7 years of age. The mAPI has the advantage that remission of asthma in the future is linked to disappearance of blood eosinophilia $<470/mm^3$ at 6 years of age (15). In addition, the presence of eosinophilia has been associated with response to topical corticosteroid at 6 years of age (16). In addition, a negative mAPI in the first 3 years of life has been shown to accurately predict 95% of those without persistent asthma between 6 and 13 years of age.

▪ TRIGGERS OF ASTHMA IN INFANTS

Care for the asthmatic infant is predicated on the correct identification of asthma versus other conditions that cause wheezing. It is critical to identify triggers, such as allergies or gastroesophageal reflux (GER), that cause asthma exacerbations. Once pertinent triggers are identified, correct therapy and ultimately long-term disease-modifying treatments can be delivered.

Passive Smoke Inhalation

Parental smoking is a profound trigger for infantile asthma. Passive smoking increases airway responsiveness in normal 4½-week-old infants (17). Overall, as much as 13% of asthma in children under 4 years of age is estimated to be secondary to maternal smoking (18). In lower socioeconomic households, children of mothers who smoke 10 cigarettes or more per day are at increased risk of asthma (19).

TABLE 20.1 UNIVERSITY OF CINCINNATI ASTHMA PREDICTIVE INDEX (UcAPI)

1. A history of two or more wheezing episodes in last 12 mo at 3-year-old clinic visit

Fetal smoke exposure during pregnancy is linked to childhood asthma and may play a larger role in the development of childhood asthma than postnatal exposure. Prenatal exposure to smoke is associated with altered pulmonary function measurements by the time children become school aged (20). In fact, this decrease in pulmonary function is noted shortly after birth in apparently normal infants. This increase in risk of asthma due to prenatal and postnatal passive smoke exposure is linked to increased risk of adult asthma (21). The most discouraging aspect to this public health problem is that maternal smoking during pregnancy is an entirely preventable cause of asthma.

Outdoor Air Pollution

Outdoor air pollution exacerbates asthma. Increased ED visits, hospitalizations, and asthma severity among children with asthma are associated with elevated pollution levels (22). Increases in hospitalization risk for children in Hong Kong are reported for every 10 $\mu g/m^3$ increase in NO_2 (23). Infants with asthma are also affected by outdoor air pollution; in fact, the number of ED-related visits was the highest in this age group (24).

Indoor Environmental Triggers

Indoor air pollution is an additional important trigger for asthma in this age group. Prevalence of asthma symptoms is highest in children whose households have open wood burning stoves (25). Other indoor air pollutants that can increase asthma triggers in infants include nitrogen dioxide produced by space

heaters and gas stoves or furnaces in improperly ventilated areas (26). Frequent use of humidifiers is associated with increased wheezing. Damp housing increases the likelihood of a diagnosis of asthma in infants and increases the hospitalization rate (27). Sensitization to mouse, presumably from indoor exposure, has been linked to increased asthma symptoms and hospitalization in very young asthmatic children (28).

Obesity

Obese asthmatic children who were diagnosed at an early age are more likely to have more cough, wheeze, chest tightness, nighttime symptoms, and lower quality of life than nonobese asthmatics who were also diagnosed with asthma at an early age (29). Obesity also contributes to higher health care costs for asthmatic children as well as increased use of asthma control medications (30). Additionally, obese asthmatic children experience more hospitalizations and ED visits for exacerbations than healthy weight asthmatic children (31). It appears that excessive infant weight gain is associated with increased risk of asthma. Among preterm infants, those infants with rapid weight gain had higher risks of asthma development (32). Another analysis of eight European birth cohorts demonstrated that rapid increase in body mass index (BMI) in the first 2 years was associated with higher asthma risk, even with adjustment for gestational age (33). Breastfeeding has been shown to reduce the risk of developing asthma and reduce the risk of becoming obese (34).

Viral Infections

In infants, viral respiratory illnesses are a major trigger for asthma. A viral trigger for status asthmatics is reported in 86% of hospitalized infants (35). Rhinovirus, respiratory syncytial virus (RSV) (36), adenovirus (37), and metapneumovirus (38) are predominant viral organisms causing wheezing in infants who present to an ED for care. In fact, the presence of asthma was related to increased risk of hospitalization during RSV infection in children less than 18 months of age (39). In addition, adenovirus is a frequent cause of wheezing in hospitalized children (17%) as demonstrated in a cohort of 2,371 children (37). The mean age of adenovirus infection was 22 months as compared to RSV at 9 months. Eleven percent of these children with adenovirus infection had a hospitalization of >7 days. Metapneumovirus causes febrile winter-time asthma exacerbations in children. Children presenting with status asthmaticus had prolonged hospitalizations when infected with metapneumovirus (38). In asthmatic children under 3 years of age, Manoha et al. (39) found that

metapneumovirus and rhinovirus were more significant viral triggers of asthma exacerbations than RSV (39). In addition, pediatric infections with picornaviruses are associated with status asthmaticus admissions to the pediatric intensive care unit (40). Cytomegalovirus infection has been noted to cause wheezing even in immunocompetent infants (41). Enterovirus D68 has been noted to cause wheezing in young children (42).

Allergy

Until recently, allergy was not considered a risk factor for the development of wheezing in infants and very young children. In 1970, Bernton and Brown (43) skin-tested allergic children to cockroach allergen and found no child under 4 years of age with a positive skin test. Other early studies also suggested that IgE-mediated allergy did not act as a trigger for infantile asthma (44). These studies have formed the groundwork for the case that allergy is unimportant to infantile asthma.

Case for Indoor Atopic Sensitization Affecting Asthma in Infants and Toddlers

Allergic sensitization now forms a core criterion in asthma predictive indices. The need for allergist input in determining aeroallergen sensitization was recently studied, and the use of clinical features alone without tests was inaccurate at predicting allergic from nonallergic asthma in children (45). In addition, the 2005 to 2006 National Health and Nutrition Examination survey revealed that information of IgE sensitization to cockroach, rat, and mold were associated with an increased risk for ED visits (46).

There are multiple regional and age-related factors involved when investigating indoor aeroallergen sources of sensitization. Delacourt et al. (47) reported that 25% of infants with recurrent wheezing had positive skin test results to either dust mites or cat allergen. The prevalence rate for reactivity to one inhalant in a general population of 1- and 6-year-old was 11% and 30%, respectively (48). Wilson et al. (49) evaluated 196 rural children less than 3 years of age diagnosed with infantile asthma for allergy. Forty-five percent of the infants who were tested to indoor inhalant allergens had at least one positive skin test result. For the 49 children who were under 1 year of age, 28.5% had a positive skin test to cockroach and 10.2% to dust mite. Environmental factors in home cooling such as evaporative coolers have been linked to higher sensitization rates in children to dust mite as compared to desert dwellers utilizing central air conditioners (50). Mouse allergy is present in 12% of asthmatic children (51). Sensitization to mouse, presumably from indoor

exposure, has been linked to increased asthma symptoms and hospitalization in very young asthmatic children (52). Cockroach sensitization is linked to previous episodes of wheezing in young children (53). In addition, 30% of rural asthmatic children may have sensitization to flying insects, such as mayfly, housefly, caddis fly, moth, and ant (54). Finally, the usefulness of identifying concurrent indoor aeroallergen sensitization was also demonstrated in the Childhood Asthma Management Program (CAMP) in which nonatopic wheezing preschoolers had remitting asthma at 4 years after study entry (55,56).

Case for Aeroallergen Sensitization to Pollen Affecting Asthma in Infants and Toddlers

Many pediatricians have been reluctant to test very young children and infants to aeroallergens. However, studies suggest that aeroallergen sensitization in very young children may in fact occur despite "common wisdom." In a birth cohort study, aeroallergen sensitized 4-year-old children had significant allergic diseases, such as asthma (52). Forty-two percent of children sensitized to grass had asthma. In addition, a majority of children were already sensitized to more than one allergen, and this increased sensitization was associated with an increased risk of asthma. Ogershok et al. (57) found that while no children under 12 months of age had aeroallergen sensitization, 29% of 12- to 24-month-olds with asthma were pollen sensitized (57). In this study, equal numbers of 3-year-old asthmatic infants and toddlers were sensitized to pollen as to indoor allergens. Overall, 40% of asthmatic children between 12 and 36 months of age were noted to be pollen sensitized. In another study, up to 52% of children less than 3 years of age with asthma were sensitized to pollen (58). This early sensitization to pollen in wheezing infants predicted subsequent asthma through adolescence (59). Studies of pediatric asthma have demonstrated that children as young as preschoolers have pollen-associated asthma symptoms, exacerbations, and hospital admissions (60).

EVALUATION OF THE PERSISTENTLY WHEEZING INFANT

Infants and young children with repeated episodes of wheezing require a complete history and physical examination. The frequency of hospitalizations and ED visits helps indicate the severity of the problem. Response to bronchodilators or maintenance inhaled corticosteroids (ICS) or use of an API may provide clues supportive of a diagnosis of asthma. Persistent coughing and wheezing associated with triggers other than viral infections strongly suggests

asthma. A history of persistent wheezing, particularly if not associated with a viral infection such as those wheezing episodes associated with exposure to pets, foods, indoor, or outdoor allergens, is an indication for skin testing. Persistently wheezing infants not responding to inhaled or systemic glucocorticosteroids or bronchodilators might need flexible bronchoscopy as suggested by 2016 American Thoracic Society (ATS) clinical practice guidelines (61), albeit this recommendation had a low quality of evidence. Factors important in the history of the coughing or wheezing infant are listed in Table 20.2. In taking an environmental history, one should remember that many infants spend significant amounts of time in more than one household.

The differential diagnosis of infantile wheezing may be complex (Table 20.3). Asthma in a child under 1 year of age is a diagnosis of exclusion because congenital defects are more prevalent in this age group. The height and weight should be compared with standard norms to determine the growth pattern. On auscultation, the presence of inspiratory wheezing may indicate extrathoracic obstruction. Wheezing due to asthma occurs throughout the entire expiratory phase. Specifically, expiratory stridor mimicking wheezing will not carry through to the end of expiration. Rales or rhonchi may indicate atelectasis or pneumonia. Unequal breath sounds may suggest diaphragmatic hernia or pneumothorax.

TABLE 20.2 IMPORTANT FACTORS IN THE HISTORY OF THE WHEEZING INFANT

HISTORY	POTENTIAL ETIOLOGY
Sudden onset	Foreign object
Intubation at birth	Subglottic stenosis, chronic lung disease of prematurity
Maternal papillomatosis	Laryngeal papilloma
Forceps delivery	Vocal cord injury
Difficulty feeding, dysphagia	Congenital heart defect
	Neurogenic defect

	Eosinophilic esophagitis
Irritability, regurgitation, torticollis	Sandifer syndrome (gastroesophageal reflux)
Recurrent pneumonia	Aspiration
	Tracheoesophageal fistula
	Cystic fibrosis
	Ciliary dyskinesia
	Immunodeficiency
	Human immunodeficiency virus infection
Formula changes	Milk or soy allergy, GERD
Isolated episode	Tuberculosis
	Respiratory syncytial virus
	Adenovirus
	Histoplasmosis
	Parainfluenza virus
	Metapneumovirus
	Mycoplasma
	Bocavirus
	Enterovirus D86
Eczema, urticaria	Atopic diseases associated with asthma
Severe or recurrent infections	Immunodeficiencies
Recurrent wheezing ≥4 episodes	Asthma

GERD, gastroesophageal reflux disease.

Infants under 1 year of age with persistent wheezing and older children with a suggestive history should be evaluated for GER, anatomic abnormalities, and

feeding disorders. An upper gastrointestinal series performed after consultation with a radiologist will provide information about anatomic abnormalities, such as diaphragmatic hernia, gastric volvulus, tracheoesophageal fistulas, and vascular rings, and may provide evidence of GER if it occurs during the examination. Feeding disorders may be diagnosed with a modified barium swallow, and the recent ATS guidelines suggest that video-fluoroscopic swallowing studies, or 24-hour pH monitoring, may be helpful in the discernment of gastrointestinal causes of wheezing (61). Dysphagia and cough with feeding may indicate eosinophilic esophagitis requiring upper endoscopy to diagnose. The most important recommendation in the 2016 ATS guideline is not to perform empiric formula switching (61). The most helpful and accurate study for the evaluation of GER in infants and small children is 24-hour esophageal pH monitoring. Bronchoscopy may also be necessary if the presence of a foreign body, aspiration, ciliary dyskinesia, or evaluation of severe infectious episode for etiologic agent. A chest film should be performed the first time an infant has an acute episode of wheezing. This will assist with evaluating nonasthmatic reasons for wheeze. Repeated radiographs for each subsequent episode of asthmatic wheezing are not necessary. In fact, a recent study demonstrated that chest X-ray in the ED for asthmatic children with exacerbation was not useful when O_2 saturations are >92% to 96%, or if afebrile in the ED (62). Other pulmonary causes of wheezing may be investigated with a sweat chloride test to exclude cystic fibrosis should be considered in any infant under 1 year of age with repeated episodes of wheezing or respiratory distress. Wheezing associated with increased numbers of severe or unusual infections should lead to evaluation for an immune deficiency. The use of a rhinoprobe or bronchoscopy may be beneficial in evaluation of infants with situs inversus totalis for primary ciliary dyskinesia (63). Tracheobronchomalacia may be determined by bronchoscopy or multidetector computed tomography as a noninvasive modality.

TABLE 20.3 DIFFERENTIAL DIAGNOSIS OF COUGHING AND WHEEZING IN INFANTS AND YOUNG CHILDREN

Congenital Disorders

Cystic fibrosis

Tracheoesophageal fistula

Primary ciliary dyskinesia

Immunodeficiency

Sickle cell disease (acute chest syndrome)

Diaphragmatic hernia

Chronic lung disease of prematurity

α_1-Antitrypsin deficiency

Pulmonary lymphangiectasia

Carnitine deficiency

Congenital Heart Disease

Aberrant left coronary artery

Chronic heart failure

Upper Airway Disorders

Foreign body (also esophageal)

Laryngotracheomalacia

Vocal cord dysfunction/paralysis, Charcot-Marie-Tooth disease, Waardenburg syndrome

Laryngeal web, papillomatosis, cleft, cyst

Subglottic or tracheal stenosis

Hemangioma

Laryngeal paralysis, Chiari malformation

Bigeminal choristoma

Lower Airway Disorders

Bronchial stenosis, casts

Foreign object

Hypersensitivity pneumonitis

Asthma

Bronchomalacia

Lobar emphysema, hemosiderosis

Infectious/Postinfectious

Epiglottitis

Croup

Tracheitis

Bronchiolitis

Diphtheria, atypical mycobacteria, pertussis

Chlamydia
Pneumocystis jiroveci
Histoplasmosis, Protozoan infection
Bronchiectasis
Rhinovirus, sinusitis
Retropharyngeal abscess
Bronchiolitis obliterans
Compression Syndromes
Tuberculosis
Lymphadenopathy
Vascular ring
Pulmonary sling, aortic malformations
Mediastinal masses
Congenital goiter
Thyroglossal duct cyst
Teratoma
Aspiration syndromes

Neurogenic	
Other	
Munchausen syndrome by proxy, psychogenic cough, child abuse	
Neurofibroma	
GERD, gastric volvulus, eosinophilic esophagitis	
Pulmonary Langerhans cell histiocytosis	

GERD, gastroesophageal reflux disease.

ALLERGY EVALUATION AND OTHER TESTS

Allergy appears to be a more significant trigger in infants and toddlers than previously appreciated. Skin testing using the prick-puncture technique with relevant indoor and outdoor ($\geq$1 year of age) should be considered in infants and young children with asthma. In fact, a history of recurrent croup (particularly if seasonal) is a nonspecific manifestation of atopy and may also suggest the need for allergy evaluation (64). Appropriate environmental control measures can then be instituted for those who are found to have evidence of atopy. Identification of outdoor aeroallergen sensitization can assist in determining issues of concomitant allergy therapy with asthma therapy and designing a maintenance asthma plan that accounts for peak pollen season.

In older preschool-aged children, fractional concentration of exhaled nitric oxide (FeNO) evaluation utilizing breath condensate technology might be useful in office evaluation of asthma. Studies have been performed showing that children as young as 3 to 4 years of age can perform this test (65). Elevated FeNO findings in these children correlated well with those of older children in the diagnosis of asthma and identifying asthma severity and aeroallergen sensitization (66). In fact, in one study of children 5 to 6 years of age, FeNO may be a more sensitive indicator of bronchial hyperresponsiveness than traditional spirometry (67).

OUTPATIENT TREATMENT OF THE ASTHMATIC INFANT AND TODDLER

The treatment of asthmatic infants is similar to that in older children and consists of avoiding identified triggers of wheezing, regular use of an anti-inflammatory medication, and a bronchodilator for symptomatic relief. However, treatment of this age group poses certain challenges. Many medications and delivery systems for asthma have been inadequately tested in this population, or there is conflicting data concerning their use. Monitoring the effectiveness of treatment in infants is more difficult owing to a lack of clinical availability of pulmonary function testing. Compliance with daily treatment is difficult because of the poor cooperation inherent in this age group as well as the reluctance of parents to have their children on medications when they are asymptomatic. Fortunately, the newer medications for asthma in infants promise better control of wheezing with improved safety and convenience. A summary of current asthma medications for infants is listed in Table 20.4.

The 2007 National Heart, Lung, and Blood Institute (NHLBI) guidelines emphasize the need for assessment of both impairment and risk (68). Impairment includes both functional limitations experienced by the patient or frequent or intense exacerbations. Functional limitations in infants can include coughing/wheezing/breathlessness during daytime, nighttime, or with play; feeding difficulties or posttussive emesis *or* use of short-acting β-adrenergic agonist >2 times/week lasting greater than 4 weeks. Possible risks to be prevented include limited lung growth *or* recurrent exacerbations of asthma with ED visit, hospitalization, and oral glucocorticosteroid use. The most difficult group to determine maintenance medication for is the infants with severe exacerbations, but no perceivable daily symptoms between episodes. The NHBLI guidelines note that children with ≥4 episodes/year that last longer than a day *and* affect sleep *and* have a positive asthma risk profile (API) should have daily long-term control therapy. Other groups of infants requiring long-term controller therapy include those with a history of two oral corticosteroid bursts for exacerbations in 6 months *or* children who require β-adrenergic agonist treatment for >2 days/week lasting longer than 4 weeks. If, at any point, a notable clinical response is not observed with asthma-specific medications, alternative diagnoses should be considered. Alternative diagnoses to asthma should be considered in children with failure to thrive, very early onset in neonatal period, vomiting, clubbing, continuous wheezing not responsive to controller therapy, hypoxia unrelated to viral illness, and no association of

symptoms with when triggers such as viral upper respiratory infection is present (68).

β-Adrenergic Agonists

β-Adrenergic agonists are clearly effective in infants and young asthmatic children for acute wheezing. Side effects of these medications may include tremors, irritability, sleep disturbances, and behavioral problems. At higher doses, tachycardia, agitation, hypokalemia, and hyperglycemia may also be seen. It has been subsequently determined that infants do have functioning β-adrenergic receptors, and studies in infants specifically diagnosed with asthma suggest that β-adrenergic agonists decrease wheezing as well as improve pulmonary functions (69). This improvement is noted both for nebulized medications and metered-dose inhalers with face mask spacer devices (70). Infants with true asthma should be given inhaled β-adrenergic agonists as needed for wheezing during acute exacerbations of their disease.

Anticholinergics

Ipratropium bromide is a quaternary isopropyl derivative of atropine available as a nebulizer solution. A pediatric asthma consensus group suggests that ipratropium may be useful as a second- or third-line medication in severe infantile asthma exacerbations. A meta-analysis of clinical trials of ipratropium for wheezing in children under 2 years of age concluded that there is not enough evidence to support the routine use of anticholinergic therapy for wheezing infants (71). A current NHLBI consensus statement notes that data suggest that ipratropium is appropriate to use during severe exacerbations in infants as add-on therapy when there is a perceived eventual need for intensive care unit admission (68). Further benefit of ipratropium treatment during the remainder of the hospitalization has not been noted.

Leukotriene Antagonists

Leukotrienes are very potent chemical mediators that produce bronchospasm, eosinophilia, stimulate mucus secretion, and increase vascular permeability, all critical features of asthma. Leukotriene antagonists block these inflammatory effects. So far, these medications appear to have a good safety profile and are well tolerated (72). Montelukast has been reported to decrease asthma exacerbations in children 10 months to 5-year-olds with intermittent asthma (73). In head-to-head comparisons to inhaled steroids in children with mild persistent asthma, both montelukast and inhaled steroids improved symptom control, but

those patients on inhaled steroids utilized less oral corticosteroid rescue (74). NHLBI asthma treatment guidelines list iICSs as preferred first-line treatment for asthma as a result of these studies. Montelukast is noted by the NIHBI guidelines to be alternative therapy or add-on therapy for mild persistent to more severe asthma (68). These recommendations do not reflect that parents of mild infantile asthmatics perceive montelukast as a particularly attractive long-term controller medication because it can be taken as a tablet once daily, it has a relatively high safety profile, and it is not a corticosteroid.

TABLE 20.4 EXAMPLES OF OFFICE-BASED MEDICATIONS FOR THE TREATMENT OF INFANTILE ASTHMA

MEDICATION	DOSAGE
Short-Course Systemic Steroids	
Prednisolone (5 mg/5 mL or 15 mg/5 mL)	1–2 mg/kg/d orally; maximum 20 mg <2 year old, 30 mg 2–5 year old
Methylprednisolone acetate (40 mg/mL; 80 mg/mL)	7.5 mg/kg intramuscularly × 1
Dexamethasone acetate	1.7 mg/kg intramuscularly
Rescue Medications[a]	
Albuterol ampules[a] (0.63 mg/3 mL; 1.25 mg/3 mL; 2.5 mg/3 mL 100 µg albuterol pMDI)	0.63 mg/3 mL–2.5 mg/3 mL saline or two puffs every 4–6 h as needed (may be dosed six puffs pMDI or 2.5 mg every 20 min × 3 doses *or* 0.15–0.3 mg/kg up to 10 mg every 1–4 h as needed *or* if transfer to ICU up to 0.5 mg/kg/h continuous nebulization for acute exacerbations)
Levalbuterol (R-albuterol)[a] (0.63 mg/3 mL; 1.25 mg/3 mL)	0.63 mg/3 mL–1.25 mg/3 mL saline every 4–6 h as needed (may be dosed 1.25 mg every 20 min for three doses then 0.075–0.15 mg/kg up to 5 mg every 1 to 4 h as

	needed)
Ipratropium (250 µg nebulized or two puffs 80 µg pMDI)	0.25–0.5 mg every 20 min × 3 (may mix with albuterol in nebulizer)
(severe exacerbation with transfer anticipated to ICU only, is not to be used as first-line therapy)	

Food and Drug Administration–Approved Maintenance Medications

Cromolyn sodium	1 amp 20 mg/2 mL nebulized 3–4 times/d
Montelukast	4 mg orally daily
Budesonide ampules[a,b]	0.25, 0.5, 1.0 mg nebulized daily
Fluticasone HFA (44, 110, or 220 µg/puff) with antistatic valved holding chamber and mask[a,c]	*Low dose*: 88–176 µg/d *Medium dose*: 176–352 µg/d *High dose*: >352 µg/d

[a] 2007 NHBLI guidelines specifically note that blow by technique for nebulized aerosol delivery is inadequate.

[b] 2007 NHBLI guidelines specifically note doubling the dose of inhaled steroid during exacerbations is not effective.

[c] 2007 NHBLI guidelines note that HFA use with spacer and face mask may reduce lung delivery by 50%.

DPI, dry-powder inhaler; HFA, hydrofluoroalkane; ICU, intensive care unit; pMDI, metered-dose inhaler.

Corticosteroids

Corticosteroids are potent anti-inflammatory medications that have profound effects on asthma. They decrease inflammatory mediators, reduce mucus production, decrease mucosal edema, and increase β-adrenergic responsiveness. Clinically, corticosteroids improve lung function, reduce airway hyperreactivity, and modify the late-phase asthmatic response. The efficacy of steroids in treating

true infantile asthma is well known. For acute exacerbations, asthmatic infants treated with steroids have a significantly reduced need for hospitalization, reduced length of stay once hospitalized, and reduced asthma medications (75,76).

Maintenance inhaled steroids provide many of the beneficial anti-inflammatory properties of corticosteroids without numerous unwanted side effects. Young children with severe asthma treated with inhaled nebulized or hydrofluoroalkane (HFA)-driven corticosteroids have markedly decreased symptoms and days of oral corticosteroid use (77). Inhaled glucocorticosteroids have been demonstrated to improve pulmonary function tests, decrease β agonist use, and improve symptoms in the youngest children with asthma (<2 years old) (78). Inhaled steroids, however, do not affect the natural history of any phenotype of asthma in the CAMP study (55). Studies of intermittent high-dose–inhaled glucocorticosteroids have been performed in children with positive API scores, but are not currently found in either the NHLBI or Global Initiative for Asthma (GINA) guidelines because of conflicting studies.

Long-Acting β-Adrenergic Agonists

NHLBI guidelines now indicate that a long-acting β-adrenergic agonist (LABA) may be useful as a maintenance drug in a fixed-dose combination with an inhaled steroid in difficult to control asthma, particularly if the child is ≥ 4 years of age. Overall, there has been a decreasing trend in the use of LABA + ICS in preschool-aged children (79). In a study including infants, fixed-dose ICS + LABA devices have been demonstrated to reduced oral steroid usage and need for short-acting β-adrenergic agonist (>6 canisters/year) (80) as compared to two separate canisters of medication. Most outcomes favor fixed-dose combination of drug usage over increasing to high-dose–inhaled steroid as suggested in NHLBI step 4 therapy for older children. This class of medication is still not a standard recommendation of the NHLBI guidelines ≤4 years of age due to lack of studies supporting efficacy.

Allergen Avoidance

Dust mite avoidance measures have been noted to have a modest treatment effect in infants and possibly reduce the prevalence of asthma in a prevention strategy devised for high-risk infants (81,82). Reduced levels of cockroach allergen have been associated with decreasing number of cockroaches by utilizing better eradication efforts (83). However, a study linking decreased cockroach levels in the dwelling with improved asthma symptoms in infants has not been reported.

Clearly, more studies are required to determine best treatment options, including allergen avoidance.

Monitoring for Obesity

Given the importance of obesity as an exacerbating factor to asthma severity, following growth charts for BMI ≥ 85% seems reasonable. Those at particular risk may be those children with repetitive oral steroid bursts (84). Those children receiving inhaled steroids can also be evaluated for longitudinal growth. Early dietary intervention with either the pediatrician or nutritionist assistance and maximized asthma care to allow for exercise may be useful strategies to prevent development of obesity in at-risk infants. In addition, encouraging breastfeeding continuation may assist in obesity risk reduction.

Allergy Immunotherapy

Potential deleterious outcomes of childhood asthma have been convincingly shown to develop despite the use of inhaled steroids. The increasingly apparent role of aeroallergens in the progression of infant wheezing to clinical long-term asthma has suggested that allergen immunotherapy might provide a more permanent disease-modifying outcome after the treatment is discontinued. In children older than 3 years of age, a 3-year course of subcutaneous immunotherapy with standardized allergen extracts has shown long-term clinical effects, including the prevention of the development of asthma in children with allergic rhinoconjunctivitis (85). This clinical effect was noted up to 7 years after treatment (84). However, subcutaneous immunotherapy in very young children is problematic because of their immaturity and inability to verbalize or cooperate. Sublingual immunotherapy might be better tolerated in young children. Data demonstrates that children as young as age 3, utilizing sublingual immunotherapy with standardized extracts might reduce symptom scores and rescue medication use in allergic asthma compared with placebo (86). Further studies are needed to determine the role of immunotherapy in altering the natural history of asthma in young children.

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Acute Severe Asthma

THOMAS CORBRIDGE AND SUSAN J. CORBRIDGE

INTRODUCTION

Each year in the United States, acute severe asthma (ASA) accounts for approximately 2.0 million emergency department (ED) visits, 480,000 hospitalizations, and 3,400 deaths (1). Although the rate of asthma death has decreased each year since 2000, African Americans and older patients with comorbid conditions remain at particular risk (2–5). Table 21.1 lists additional risk factors for near-fatal or fatal asthma.

Treatment of an acutely ill patient with asthma involves targeted strategies to improve airway obstruction and decrease work of breathing. For most patients, short-acting β agonists (with or without a short-acting anticholinergic) and a burst of systemic corticosteroids are sufficient. Patients with acute respiratory failure require supplemental oxygen and supported ventilation by mask or endotracheal tube (5–7). Adherence with evidence-based asthma guidelines for hospitalized patients has improved over recent years, although substantial interhospital variability exists, and this has improved outcomes (8). Comprehensive management of this patient group includes education, vaccinations, controller agents, and follow-up appointments with an asthma specialist.

PATHOPHYSIOLOGY OF ACUTE AIRFLOW OBSTRUCTION

The speed with which ASA develops varies (9). A sudden attack that leads to severe obstruction in less than 3 hours is termed sudden asphyxic asthma. This type of attack represents a more pure form of smooth muscle–mediated bronchospasm and may respond quickly to bronchodilators (10,11). Triggers of sudden attacks include medications, such as nonselective nonsteroidal anti-inflammatory agents and β-blockers in susceptible patients, allergen or irritant exposure, sulphites, and inhalation of illicit drugs (12,13). Respiratory tract infection is not a common cause (14).

TABLE 21.1 RISK FACTORS FOR NEAR-FATAL OR FATAL ASTHMA

Frequent emergency department visits
Frequent hospitalization
Intensive care unit admission
Intubation
Hypercapnia
Barotrauma
Psychiatric illness
Medical noncompliance
Illicit drug abuse
Low socioeconomic status
Inadequate access to medical care
Inadequate asthma control/the use of more than two canisters per month of inhaled β_2-adrenergic agonist
Poor patient perception of airflow obstruction
Comorbidities such as coronary artery disease
Sensitivity to *Alternaria* species

More commonly, exacerbations evolve over 24 hours or more with progressive airway wall inflammation, accumulation of intraluminal mucus, and bronchospasm. Mucus, which consists of sloughed epithelial cells, eosinophils, fibrin, and other serum components that have leaked through the denuded airway epithelium, obstructs large and small airways and predicts a more protracted course. Patients with slower onset exacerbations have time to intervene with corticosteroids, an opportunity that is too often missed, resulting in the need for emergency services. Triggers of slower exacerbations include viral infections and allergic and nonspecific irritant exposures.

Regardless of tempo, severe airflow obstruction increases work of breathing and interferes with gas exchange. The higher mechanical cost of breathing in these patients is because of greater amounts of resistive work from narrowed airways and elastic work from lung hyperinflation. Whereas bronchospasm and inflammation underlie airway narrowing, inadequate expiratory time and incomplete exhalation cause lung hyperinflation. A patient with a respiratory rate in the 20s or 30s has 1 or 2 seconds for exhalation. This amount of time is inadequate to exhale tidal breaths in the setting of airflow obstruction. Lung volumes increase, and tidal breathing occurs at higher lung volumes (even near total lung capacity in severe cases) where the compliance of the lung is low. This dynamic lung hyperinflation (DHI) may be self-limiting because hyperinflation increases lung elastic recoil pressure and airway diameter to increase expiratory flow. At the end of exhalation, incomplete gas emptying elevates alveolar volume and pressure, a state referred to as auto–positive end-expiratory pressure (auto-PEEP). To affect inspiratory flow, patients must be able to overcome auto-PEEP. Their ability to do so is adversely affected by DHI, which places the diaphragm in an unfavorable position for force generation. Fatiguing muscles and respiratory acidosis further decrease respiratory muscle strength (15). In the end, the combination of diminished respiratory muscle strength and inordinate resistive and elastic loads can cause hypercapnic respiratory failure and respiratory arrest.

Airway narrowing further decreases ventilation (V) relative to perfusion (Q) in alveolar-capillary units, resulting in hypoxemia (16). Asthma generally does not cause intrapulmonary shunt physiology, which is defined by a V/Q of zero in alveolar-capillary units. Common causes of shunt are pneumonia, pulmonary edema, alveolar hemorrhage, and atelectasis. When significant, patients with shunt are difficult to oxygenate. Asthma drops V/Q, but not to zero, and therefore, patients with asthma usually respond to supplemental oxygen, and refractory hypoxemia suggests other diagnoses. Although there is a rough

correlation between the hypoxemia and the severity of airflow obstruction, hypoxemia may occur sooner and/or resolve later than measures of obstruction (i.e., peak flow or spirometry) (17).

Cardiovascular complications of ASA include accentuation of the normal inspiratory reduction in stroke volume and blood pressure, termed the *pulsus paradoxus* (PP). The vigorous inspiratory efforts required to overcome auto-PEEP drop pleural pressure and increase blood return to the right ventricle (RV). The RV fills early in inspiration and shifts the intraventricular septum leftward, causing diastolic dysfunction of the left ventricle (LV) and incomplete LV filling. Large negative pleural pressures further impair LV emptying by increasing LV afterload (18). Rarely, these effects cause pulmonary edema. During forced exhalation, positive pleural and intrathoracic pressures decrease venous return to the RV. These swings in pleural pressure and cyclical changes in venous return underlie widened PP and signal a severe attack. However, the absence of a widened PP does not ensure a mild attack because PP decreases in the fatiguing patient unable to generate large swings in pleural pressure. Further complicating severe attacks is the potential for DHI to increase total pulmonary vascular resistance, pulmonary artery pressures, and cause right heart strain (19).

CLINICAL PRESENTATION, DIFFERENTIAL DIAGNOSIS, AND SEVERITY ASSESSMENT

Analysis of multiple factors, including the history, physical examination, measures of airflow obstruction, response to therapy, arterial blood gases, and chest radiography, is important in the assessment and management of acutely ill patients (20,21).

Differential Diagnosis

"All that wheezes is not asthma" is a fitting clinical saw worth considering during the initial evaluation. An extensive smoking history suggests *chronic obstructive pulmonary disease* and a more fixed form of expiratory airflow obstruction. *Congestive heart failure* may present with wheezing (termed *cardiac asthma*) that responds to bronchodilators (22). *Myocardial ischemia* should be considered in patients at risk for coronary artery disease, particularly those receiving subcutaneous or intramuscular epinephrine, because ASA can incite an imbalance between myocardial oxygen supply and demand (23). *Aspiration and foreign body obstruction* occasionally mimic asthma, and should be considered in the very young and old, in patients with altered mental status or

neuromuscular disease, and when symptoms occur after eating or dental work. Localized wheeze and, rarely, asymmetric hyperinflation on chest radiography are clues to foreign body aspiration. *Upper airway obstruction*, including vocal cord dysfunction (VCD), can present with respiratory distress and "wheezes." In contrast to asthma, classic upper airway (extrathoracic) obstruction flattens the inspiratory portion of the flow-volume loop and is associated with prolongation of inhalation and stridor. Other clues to the presence of VCD include normal oxygenation, lack of response to bronchodilators, and normal airway pressures after intubation (24). Significant response to helium–oxygen mixtures (heliox) suggests upper airway obstruction, although heliox response occurs in some patients with asthma and does not reliably distinguish upper from lower airway obstruction. *Tracheal stenosis* should be considered in patients with a history of intubation, trauma or radiation to the throat or chest, sarcoidosis, granulomatosis with polyangiitis, amyloidosis, and benign or malignant tumors. Whereas mycobacterial and viral *infections* can present with wheezing, bacterial pneumonia is an unusual cause of wheezing. Antibiotics are frequently prescribed for patients with asthma with increased sputum production alone, but have not been shown to improve outcome (25,26). Wheezing has been reported in *pulmonary embolism* (27); pulmonary embolism should be considered in a patient with risk factors for venous thromboembolism, particularly in the absence of known asthma.

Physical Examination

The general appearance of the patient (posture, speech, positioning, and alertness) provides a quick guide to severity, response to therapy, and need for intubation. Patients assuming the upright position have a higher heart rate, respiratory rate, and PP, and a significantly lower partial pressure of arterial oxygen (PaO$_2$) and peak expiratory flow rate (PEFR) than patients who are able to lie supine (28). Diaphoresis is associated with an even lower PEFR. Accessory muscle use indicates a severe attack, but is not always present (29). An altered mental status and bradycardia suggest impending arrest and are indications for intubation (21).

The mouth and neck should be inspected for evidence of previous surgery, malignancy, and angioedema. Prolongation of inspiration and stridor suggest upper airway obstruction. Tracheal deviation, asymmetric breath sounds, mediastinal crunch, and subcutaneous emphysema suggest barotrauma and the need for a stat chest X-ray.

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Chest auscultation typically reveals expiratory-phase prolongation and wheezing that is more pronounced during exhalation than inhalation. However, wheezing is not a reliable indicator of severity (30). A silent chest indicates severely decreased air exchange and possible impending respiratory arrest. (In this situation, increased wheezing signals improvement.) Localized wheezing or crackles may represent mucus plugging and atelectasis, but should prompt consideration of pneumonia, pneumothorax, endobronchial lesions, and foreign body.

Tachycardia is common (31). Heart rate generally decreases in improving patients, but can remain elevated despite clinical improvement because of β_2-adrenergic agonists. The usual rhythm is sinus tachycardia, but supraventricular and ventricular arrhythmias occur; bradycardia is an ominous sign (21).

Measurement of Airflow Obstruction

Measuring PEFR or forced expiratory volume in 1 second (FEV_1) helps assess the severity of airflow obstruction. Objective measures are important because physician estimates of severity are often wrong—with errors equally distributed between overestimates and underestimates of the actual PEFR. However, PEFRs should not be measured in severely ill patients because they rarely alter management, and the required maneuver can worsen bronchospasm even to the point of respiratory arrest (32).

According to the Expert Panel Report 3 of the National Institutes of Health, mild attacks are characterized by PEFR > 70% of predicted or personal best, moderate attacks by PEFRs between 40% and 69%, severe attacks by PEFR < 40%, and life-threatening attacks by PEFR < 25% (21). Measuring the change in PEFR or FEV_1 is a valid predictor of the need for hospitalization. Several studies have demonstrated that inconsequential changes or deterioration after 30 to 60 minutes of therapy predict a more severe course and need for hospitalization, whereas a robust response typically allows for discharge (33).

Arterial Blood Gases

Arterial blood gases document the degree of hypoxemia and allow for acid–base analysis. In the early stages of ASA, mild hypoxemia and respiratory alkalosis are common. As the severity of airflow obstruction increases, $PaCO_2$ generally increases, and therefore, eucapnia and hypercapnia are worrisome findings. Hypercapnia alone is not an indication for intubation because these patients may still respond adequately to pharmacotherapy and/or noninvasive mechanical

ventilation (NIV) (34,35). Conversely, the absence of hypercapnia does not rule out a life-threatening attack (36).

Arterial blood gases are not required in all patients, especially patients who respond clinically to initial treatment, and in an attempt to limit the complications of arterial puncture, venous blood gases are commonly used in EDs to screen for arterial hypercapnia. Data suggest that arterial hypercapnia is extremely unlikely when the venous PCO_2 is ≤45 mm Hg (37).

Patients with respiratory alkalosis lasting days compensate by wasting serum bicarbonate, which may manifest as a normal anion gap metabolic acidosis (referred to as posthypocapnic metabolic acidosis). Metabolic acidosis with an elevated anion gap typically results from lactic acidosis secondary to increased work of breathing, tissue hypoxia, or intracellular alkalosis. Lactic acidosis indicates a severe exacerbation and occurs more commonly in men and in patients receiving parenteral β_2-adrenergic agonists (38).

Serial blood gases are not necessary to determine clinical course. In most cases, valid judgments follow serial examinations with attention to patient posture, accessory muscle use, diaphoresis, chest auscultation, pulse oximetry, and PEFR measurements. Patients who deteriorate on these grounds are candidates for intubation regardless of $PaCO_2$. Conversely, intubation is not indicated in patients improving by multifactorial assessment despite hypercapnia. Serial blood gases help guide management in mechanically ventilated patients.

Chest Radiography

In classic cases of ASA, chest X-rays rarely alter management (39). In one study reporting radiographic abnormalities in one-third of cases, the majority of findings were attributable to common asthma features of airway wall thickening and intraluminal mucus (40). Chest radiography is indicated for patients with localizing signs or symptoms and when the diagnosis is in question. In mechanically ventilated patients, chest radiography further confirms proper endotracheal tube position and helps to exclude barotrauma.

EMERGENCY DEPARTMENT MANAGEMENT

Patients with mild-to-moderate attacks responding well to initial therapy may be considered for discharge. Observation in the ED for at least 60 minutes after the last β_2-adrenergic agonist treatment ensures suitability for discharge (21).

Patients should invariably be discharged on inhaled and/or systemic steroids and receive written medication instructions, a written asthma action plan, and instructions for follow-up. Patients presenting with a mild exacerbation that completely resolves after bronchodilators may be discharged on inhaled steroids or the combination of a long-acting β_2-adrenergic agonist and inhaled steroid, particularly if they were not previously on controller therapy. Patients with incomplete responses or attacks of greater severity should receive a course of intramuscular or oral steroids. When considering hospitalization, health care providers should err on the side of admission when there is a risky home environment or noncompliance favors directly observed therapy.

Patients with severe attacks who do not respond (or actually deteriorate) in the face of initial bronchodilator therapy should receive systemic steroids and be admitted to the hospital. Indications for intensive care unit admission include respiratory arrest, progressive hypercapnia, NIV and invasive mechanical ventilation, altered mental status, arrhythmias, myocardial injury, and need for frequent bronchodilator treatments (21).

PHARMACOLOGIC THERAPY

Oxygen

Supplemental oxygen by low-flow nasal cannula or facemask should be titrated to maintain arterial oxygen saturations greater than 92% (>94% with pregnancy and ischemic heart disease). Adequate oxygenation is generally not difficult to achieve with low-flow supplementation and is important for delivery of oxygen to tissues, including the exercising respiratory muscles, heart, and brain. Supplemental oxygen further protects against hypoxemia resulting from β_2-adrenergic agonist–induced pulmonary vasodilation and increased blood flow to low V/Q units (41).

β_2-Adrenergic Agonists

Inhaled short-acting β_2-adrenergic agonists are the primary treatment of smooth muscle–mediated bronchoconstriction. Approximately two-thirds of patients with ASA respond convincingly to this therapy in the ED. The other third requires prolonged treatment in the ED or admission to hospital. In a study by Rodrigo and Rodrigo, 67% of patients improved significantly and were discharged from the ED after 2.4 mg albuterol by metered-dose inhaler (MDI) (42). Half of the responders in this study met discharge criteria after receiving 12

puffs (1.2 mg) of albuterol. Similarly, Strauss and co-workers found that two-thirds of patients with acute asthma could be discharged after three 2.5-mg doses of albuterol by nebulization every 20 minutes (43).

The optimal dose of albuterol in ASA has yet to be firmly established. McFadden and colleagues compared two 5.0-mg nebulized treatments of albuterol over 40 minutes with the standard approach of three 2.5-mg albuterol every 20 minutes in 160 ED patients (44). Although both approaches were effective, the 5.0-mg regimen increased lung function quicker and to a greater extent than standard-dose therapy. The higher dose strategy resulted in patients achieving discharge criteria more rapidly and leaving the ED with PEFRs closer to normal, and a trend toward fewer hospitalizations. On the other hand, Emerman and colleagues compared the effects of three doses of 2.5 or 7.5 mg of albuterol every 20 minutes in 160 acutely ill patients with asthma and found no differences in spirometry or admission rates (45).

These data generally support the standard recommendation of administering 2.5-mg albuterol by nebulization every 20 minutes during the first hour of treatment (i.e., three doses) (21). MDIs are also effective. Also, 4 to 12 puffs by MDI with a spacing device achieves the same degree of bronchodilation as one 2.5-mg nebulized treatment of albuterol (46). MDIs with spacers are less expense and faster; hand-held nebulizers require fewer instructions, less supervision, and less coordination.

Continuous or repetitive doses of albuterol are indicated until there is convincing improvement or side effects limit further administration (Table 21.2) (47). Fortunately, high doses of inhaled β_2-adrenergic agonists are generally well tolerated. Tremor and tachycardia are common, but significant cardiovascular morbidity is rare (48). Clinical response and side effects further inform the dosing schedule after the first hour of management.

Racemic albuterol consists of equal amounts of R- and S-albuterol. The R isomer confers bronchodilator effects, whereas the S isomer is either inert or pro-inflammatory, which provides the rationale for using the R isomer alone. The R isomer levalbuterol compares favorably to albuterol, but is not superior (49,50).

Long-acting β_2-adrenergic agonists are not indicated in the initial treatment of ASA, although formoterol (which has acute onset of action) is safe and effective in this setting (51). The combined inhalers containing long-acting β_2-adrenergic agonists and inhaled corticosteroids (ICSs) can be initiated or continued in hospitalized patients receiving rescue therapy, and will generally be required to

achieve adequate control in the outpatient setting (52).

TABLE 21.2 COMMON DRUGS USED IN THE INITIAL TREATMENT OF ACUTE ASTHMA IN ADULTS	
Albuterol	2.5 mg in 2.5 mL normal saline by nebulization every 20 min three times over the first hour; or four to eight puffs by MDI with spacer every 20 min three times; for intubated patients, titrate to physiologic effect and side effects.
Ipratropium bromide	0.5 mg by nebulization every 20 min three times in combination with albuterol, or four to eight puffs by MDI with spacer every 20 min for three doses.
Epinephrine	0.3 mL of a 1:1,000 solution subcutaneously every 20 min three times as needed
Corticosteroids	Prednisone or methylprednisolone 40–80 mg/d in 1 or 2 divided doses until PEFR reaches 70% of predicted or the patient's personal best.

MDI, metered-dose inhaler; PEFR, peak expiratory flow rate.

There is no advantage to parenteral administration of β_2-adrenergic agonists in the initial management of ASA unless the patient is unable to comply with inhaled therapy (such as those with altered mental status and impending cardiopulmonary arrest). However, lack of response to several hours of inhaled β_2-adrenergic agonist therapy is an indication for subcutaneous or intramuscular epinephrine, which is generally well tolerated (53,54). Intravenous (IV) β_2-adrenergic agonists are not recommended, with the possible exception of patients in cardiac arrest. They are less effective and more toxic than their inhaled counterparts (55).

Ipratropium Bromide

The bronchodilating properties of ipratropium bromide are modest, precluding its use as a single agent in ASA. However, data support adding ipratropium to albuterol in the initial management of *severe* cases of ASA. In these cases, combination therapy decreases time in the ED, albuterol dose requirements, and hospitalization rates (56–59). The benefits of combination therapy do not extend

to patients with mild-to-moderate exacerbations (59–62). The current recommendation is to mix 0.5 mg of ipratropium bromide with 2.5 mg of albuterol in the same nebulizer and deliver three treatments over the first hour to patients in severe exacerbation (21). A similar strategy is available by MDI with spacer. Once the patient is admitted, there are no data to support continued combination therapy, and albuterol can be used alone as required (63,64).

Corticosteroids

Systemic corticosteroids are indicated in patients with ASA except for the rare patient demonstrating a robust and durable response to inhaled β_2-adrenergic agonists alone. Corticosteroids treat inflammation by promoting new protein synthesis, and their effects are delayed, underlining the importance of early initiation. This delay may explain the results of select studies demonstrating that corticosteroid use in the ED does not improve lung function acutely or decrease hospitalization rates (65). A number of other studies have demonstrated that given early systemic steroids decrease hospitalization rates (66–68), speed the rate of recovery, and decrease the chance of relapse after discharge (69–72).

Different routes of administration and dosing regimens have been studied (73–77), and debate continues regarding the optimal strategy. Oral steroids are as effective as parenteral steroids (77). For hospitalized adults, the Expert Panel Report 3 recommends 40 to 80 mg/day of prednisone, methylprednisolone, or prednisolone in 1 or 2 divided doses until PEFR reaches 70% of predicted or the patient's personal best (21). For outpatients, a common strategy is to use prednisone, 40 mg/day for 5 to 10 days, with early follow-up to judge clinical response and optimize the outpatient regimen (74). Recently, a single 12-mg dose of oral dexamethasone was shown to be noninferior to 60 mg/day of prednisone for 5 days (75). Alternatively, a single dose of triamcinolone diacetate 40 mg intramuscularly has also been reported to be as effective as prednisone 40 mg/day for 5 days (76).

There is no established role for use of high-dose ICSs in acute asthma in patients receiving systemic steroids (78). However, ICSs play a pivotal role in achieving outpatient asthma control, and patients with ASA discharged from the ED or hospital should be on an ICS–based treatment program.

Theophylline and Aminophylline

Overall, the data do not support the use of theophylline or aminophylline in ASA. Nair et al. (79) conducted a meta-analysis for the *Cochrane Review* and

concluded that the use of IV aminophylline does not result in additional bronchodilation in adults compared to standard therapy with inhaled short-acting β_2-adrenergic agonists and that the frequency of adverse effects was higher with aminophylline use. The Expert Panel Report 3 does not recommend the use of theophylline for adults or children in the ED or hospital setting (21).

Serum levels should be checked on arrival in patients taking theophylline as an outpatient before additional drug is prescribed. If the serum level is therapeutic and adverse effects have not been identified, then theophylline may be continued orally or by continuous infusion.

Magnesium Sulfate

Prospective trials and meta-analyses have yielded conflicting results regarding the efficacy of magnesium sulfate ($MgSO_4$) in ASA. A recent meta-analysis of the safety and efficacy of IV $MgSO_4$ in adults treated in the ED for ASA demonstrated that a single infusion of 1.2 or 2 g IV $MgSO_4$ over 15 to 30 minutes reduces hospital admissions and improves lung function in patients who had not responded to supplemental oxygen, β agonists, and IV corticosteroids (80). There is no established role for inhaled $MgSO_4$ in acute asthma (81).

Leukotriene Modifiers

Limited data support the use of leukotriene receptor antagonists in ASA. The most compelling study is a randomized, double-blinded, parallel group trial by Camargo et al. (82) in 201 acutely ill patients with asthma. When added to standard therapy, IV montelukast (which is not available in the United States) improved FEV_1 over the first 20 minutes compared to placebo. Effects were seen within 10 minutes and lasted for 2 hours. There is no benefit to adding oral montelukast to conventional therapy (83).

Heliox

Heliox consists of 20% oxygen and 80% helium (30%:70% mixtures are also available). It is a low-density gas that can be delivered by face mask in an attempt to decrease work of breathing or as a driving gas for albuterol nebulization. Rarely, experienced clinicians may use heliox in intubated patients with refractory and life-threatening exacerbations. The data have demonstrated mixed but disappointing results with heliox, and methodologic differences, small patient numbers, and failure to control for upper airway obstruction have confounded these studies (84–86). Overall, the data do not support the routine

use of heliox in ASA; however, it is reasonable to consider its use in severe cases (84,87).

Antibiotics

The Expert Panel does not recommend antibiotics for most patients with acute asthma unless necessary to treat comorbid conditions, such as pneumonia or bacterial sinusitis (21). In the recently published randomized Azithromycin for Acute Exacerbations of Asthma trial, azithromycin was no better than placebo regarding symptoms, quality of life, or lung function (26). The main reason for nonrecruitment in this study was receipt of antibiotics in almost half of screened patients, suggesting that clinicians are not adhering to guideline recommendations in many cases.

MECHANICAL VENTILATION

Noninvasive Positive Pressure Ventilation

Despite the increasing use of NIV in patients with acute asthma managed in EDs and intensive care units, limited data are available to inform its use in this setting. A recent meta-analysis on the use of NIV for ASA demonstrated decreased fatigue, improved gas exchange, and decreased risk of intubation (34), and NIV is now approximately as common as invasive ventilation for initial ventilator support (88). Mortality from asthma is less in patients receiving NIV compared to patients requiring intubation, but there is concern about increased mortality in the small subgroup of patients failing NIV and subsequently requiring intubation. This may stem in part from delayed recognition of the need for intubation (88).

NIV should be considered only in alert, cooperative, and hemodynamically stable patients. It should be used only by experienced staff in a highly monitored setting, allowing for early identification of failing patients. Reasonable initial settings are inspiratory positive airway pressure (IPAP) 8 to 10 cm H_2O and expiratory positive airway pressure (EPAP) 0 to 5 cm H_2O delivered by full face mask. Depending on the patient's initial clinical response, IPAP can be increased to 12 to 15 cm H_2O and EPAP to 5 cm H_2O to decrease respiratory rate, work of breathing, and dyspnea.

Intubation

Despite optimal use of medications and NIV, a small proportion of patients with

ASA require intubation for respiratory arrest and impending respiratory arrest (e.g., extreme exhaustion, a quiet chest, bradycardia, or altered mental status).

Postintubation Hypotension

The immediate postintubation period can be challenging, and considerable care must be taken to stabilize the patient through the thoughtful use of sedatives, bronchodilators, fluids, and ventilator settings. One immediate concern in the postintubation period is the potential for hypotension (89). Hypotension occurs for several reasons, including sedation, loss of sympathetic activity, and hypovolemia from increased insensible losses and decreased oral fluid intake. Overzealous Ambu-bag ventilation or inappropriately set respiratory rates on the ventilator also result in dangerous levels of DHI and elevated airway pressures. This decreases venous return to the RV, decreases LV filling, stroke volume, and cardiac output. When this occurs, a 30- to 60-second trial of hypopnea (2 to 3 breaths/minute) or apnea in a preoxygenated patient is both diagnostic and therapeutic (89). This maneuver prolongs expiratory time and deflates the lung to improve hemodynamics. Failure of a trial of deflation to improve hemodynamic stability mandates consideration of tension pneumothorax and tube thoracostomy. Hemodynamic improvement with deflation does not completely exclude tension pneumothorax, requiring careful inspection of the postintubation chest X-ray.

Initial Ventilator Settings and Dynamic Hyperinflation

Expiratory time, tidal volume, and severity of airflow obstruction determine the level of DHI (89). Because airflow obstruction is generally refractory in this subgroup of patients, expiratory time and tidal volume are the key manipulable variables during ventilator management. Expiratory time is determined by minute ventilation (respiratory rate × tidal volume) and inspiratory flow rate (90,91). When minute ventilation is increased, expiratory time is decreased and DHI increases. To avoid dangerous levels of DHI, the initial minute ventilation should not exceed 7 to 8 L/minute in a 70-kg weighing patient (92). To this end, we recommend a respiratory rate of 12 to 14 breaths/minute and a tidal volume of 7 to 8 mL/kg.

High inspiratory flow rates can further prolong expiratory time, but in patients breathing over the set ventilator rate, increasing the inspiratory flow rate can increase respiratory rate, mandating a close watch on measures of lung inflation (93). During volume-controlled mechanical ventilation (VCV), we favor an inspiratory flow rate of 60 L/minute, using a square flow pattern (i.e., a constant

flow rate). A decelerating flow strategy with an average flow of >40 L/minute is an acceptable alternative in many patients, and may be better tolerated.

There is no consensus as to which ventilator mode should be used in patients with asthma. In paralyzed patients, synchronized intermittent mandatory ventilation and assist-controlled ventilation are equivalent. VCV is more commonly used than pressure-controlled ventilation (PCV), but theoretically, PCV may deliver more uniform distribution of ventilation than VCV. On the other hand, the delivered Vt is more variable during PCV and is affected by changes in the degree of lung inflation and bronchoconstriction.

Ventilator-applied PEEP is not recommended in sedated and paralyzed patients because it may increase lung volume if used excessively (94). In spontaneously breathing patients, small amounts of ventilator-applied PEEP (e.g., 5 cm H_2O) decrease inspiratory work of breathing by decreasing the pressure gradient required to overcome auto-PEEP and are safe.

Assessing Lung Inflation

Determination of the severity of DHI is central to risk assessment and adjustment of ventilator settings. Numerous methods have been proposed to measure DHI. The volume at end-inspiration, termed Vei, is determined by collecting expired gas from total lung capacity to functional residual capacity during 40 to 60 seconds of apnea in a paralyzed patient. A Vei greater than 20 mL/kg has been correlated with barotrauma (92). Indeed, Vei is the only measure of DHI that has been shown to predict barotrauma (even though it may underestimate the degree of air trapping with very slowly emptying air spaces). The limitation with this measure is that it is impractical in clinical practice, and most clinicians and respiratory therapists are unfamiliar with expiratory gas collection.

Surrogate measures of lung inflation include the single-breath plateau pressure (Pplat) and auto-PEEP. Accurate measurements of these pressures require patient–ventilator synchrony and absence of patient effort. Even when measured accurately, neither pressure has been proved to predict complications.

Pplat is an estimate of average end-inspiratory alveolar pressures determined by stopping flow at end-inspiration. Pplat is affected by the entire respiratory system, including lung tissue and chest wall; thus, significant variations in DHI may occur from patient to patient at the same pressure. For example, an obese patient will likely have a higher Pplat than a thin patient for the same degree of DHI. Common recommendations are to seek a Pplat < 30 cm H_2O.

Auto-PEEP is the lowest average alveolar pressure achieved during the respiratory cycle. It is obtained by measuring airway-opening pressure during an end-expiratory hold maneuver. In the presence of auto-PEEP, airway-opening pressure increases by the amount of auto-PEEP present. Persistence of expiratory gas flow at the beginning of inspiration (which can be detected by auscultation or monitoring of flow tracings) also suggests auto-PEEP. Auto-PEEP may underestimate the severity of DHI (95). This occurs when severe airway narrowing limits the communication between the alveolus and mouth so that during an end-exhalation hold maneuver, airway-opening pressure fails to increase. Without supporting data, a common goal in clinical practice is to seek an auto-PEEP of less than 15 cm H_2O.

Ventilator Adjustments

With the above considerations in mind, we offer the following algorithm for ventilator adjustment. This algorithm relies on Pplat as the measure of DHI and arterial pH as a marker of ventilation. If initial ventilator settings result in Pplat of more than 30 cm H_2O, respiratory rate should be decreased until this goal is achieved. Hypercapnia may ensue, but fortunately, this is generally well tolerated (96). Anoxic brain injury and myocardial dysfunction are contraindications to permissive hypercapnia because hypercapnia causes cerebral vasodilation, decreased myocardial contractility, and pulmonary vasoconstriction (97). If hypercapnia results in a blood pH of less than 7.15 (and respiratory rate cannot be increased because of the Pplat limit), we consider a slow infusion of sodium bicarbonate, although this has not been shown to improve outcome. If Pplat is less than 30 cm H_2O and pH is less than 7.20, respiratory rate can be safely increased to lower $PaCO_2$ and elevate arterial pH until Pplat nears the threshold pressure. Commonly, patients can be ventilated to a pH of more than 7.20 with a Pplat of less than 30 cm H_2O, particularly as they improve and near extubation.

Whether the above strategy improves outcomes is unknown. One study of barotrauma in patients mechanically ventilated with limited tidal volumes and airway pressures included 79 patients with asthma; five of these patients developed barotrauma (98). There were no reported differences in tidal volumes and airway pressures between patients with and without barotrauma.

Sedation and Paralysis

Sedation is indicated to improve comfort, safety, and patient–ventilator

synchrony. This is particularly true when hypercapnia stimulates respiratory drive. Some patients (such as those with sudden asphyxic asthma) may be extubated within hours. In these patients, propofol is attractive because it can be rapidly titrated to a deep level of sedation and still allow for quick awakening after discontinuation (99). Time to awakening is less predictable with benzodiazepines, and benzodiazepines increase the risk of delirium. To provide the best combination of amnesia, sedation, analgesia, and suppression of respiratory drive, we typically add fentanyl to propofol. Consideration should be given to holding sedatives and analgesics in calm patients to avoid accumulation (100).

Ketamine, an IV anesthetic with sedative, analgesic, and bronchodilating properties, is generally reserved for intubated patients with severe bronchospasm precluding safe mechanical ventilation (101). Ketamine must be used with caution because of its sympathomimetic effects and association with delirium.

Short-term paralysis is indicated when safe and effective mechanical ventilation cannot be achieved by sedatives and analgesics. Cis-atracurium is the preferred agent because it is essentially free of cardiovascular effects, does not release histamine, and does not require hepatic and renal function for clearance. Paralytics may be given intermittently by bolus or continuous IV infusion. Continuous infusions require a nerve stimulator or withholding the drug every 4 to 6 hours to avoid accumulation and prolonged paralysis. Paralytic agents should be minimized whenever possible because of increased risk of deep vein thrombosis, pneumonia, and myopathy (102).

Administration of Bronchodilators during Mechanical Ventilation

Many questions remain regarding the optimal administration of inhaled bronchodilators during mechanical ventilation. Manthous et al. (103) compared the efficacy of albuterol delivered by MDI via a simple inspiratory adapter (no spacer) to nebulized albuterol in mechanically ventilated patients. Using the peak-to-pause pressure gradient at a constant inspiratory flow to measure airway resistance, they found no effect (and no side effects) from the administration of 100 puffs (9.0 mg) of albuterol; whereas albuterol delivered by nebulizer to a total dose of 2.5 mg reduced inspiratory flow-resistive pressure by 18%. Increasing the nebulized dose to a total of 7.5 mg reduced airway resistance further in most patients, but caused side effects in half of these patients. When MDIs are used during mechanical ventilation, they must be delivered by a

spacing device on the inspiratory limb of the ventilator (104). In general, nebulizers should be placed close to the ventilator, and in line humidifiers stopped during treatments. Inspiratory flow should be reduced to approximately 40 L/minute during treatments to minimize turbulence, although this strategy has the potential to worsen lung hyperinflation and must be time limited. Patient–ventilator synchrony is crucial to optimize drug delivery. In either case (MDI with spacer or nebulizer), higher drug dosages are required. Dose should also be titrated to achieve a decrease in the peak-to-pause airway pressure gradient. If no measurable decrease in airway resistance occurs, other causes of elevated airway resistance, such as a plugged endotracheal tube, should be considered.

Other Considerations

Rarely, the above strategies are unable to stabilize the ventilated patient, and consideration should be given to the use of other strategies. Halothane and enflurane are general anesthetic bronchodilators that can reduce airway pressures and $PaCO_2$ (105), but these agents cause myocardial depression, arterial vasodilation, and arrhythmias, and their benefits do not last after drug discontinuation. Heliox delivered through the ventilator circuit may also decrease airway pressures and $PaCO_2$ (106). However, safe use of heliox in ventilated patients requires significant institutional expertise and careful planning. Ventilator flow meters that are gas density dependent must be recalibrated to low-density gas, and a spirometer should be placed on the expiratory port of the ventilator during heliox administration to measure tidal volume. Finally, extracorporeal life support is a viable option in many centers for patients with life-threatening ASA despite optimal pharmacologic and ventilator management.

Extubation

Although some patients with labile asthma respond to therapy within hours, more typically patients require 24 to 48 hours of bronchodilator and anti-inflammatory therapy before they are candidates for extubation. Although weaning and extubation criteria have not been validated in ASA, a reasonable approach is to offer a spontaneous breathing trial to alert or easily arousable patients who have (1) minimal oxygen requirements, (2) normalized their $PaCO_2$, (3) require infrequent suctioning, and (4) hemodynamically stable. If pneumonia, anoxic brain injury, or muscle weakness has not complicated the patient's course, progression to spontaneous breathing should be prompt. Patients successfully completing a 30- to 120-minute spontaneous breathing trial

can evaluated for extubation. A cuff leak test helps assess patency of the upper airway at the time of extubation. After extubation, observation in the intensive care unit is recommended for an additional 12 to 24 hours, and attention appropriately shifts to optimizing outpatient control and preventing future attacks.

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Asthma Clinical Trials

PEDRO C. AVILA

Clinical trials are the gold standard to prove efficacy of new therapies and management approaches for any disease. These trials take place after several years of preclinical development of new drugs designed to interfere with disease pathogenesis. Drugs vary widely from low-molecular-weight molecules to large recombinant compounds, such as monoclonal antibodies. Once a candidate drug is selected for development, it undergoes several toxicology tests before the Food and Drug Administration (FDA) approves it for investigational studies in humans. Under FDA supervision, clinical development takes place through phases I, II, and III studies to learn the pharmacokinetics (PK), pharmacodynamics (PD), and clinical efficacy of the new drug, respectively, while accumulating safety data all along. Several drugs have been developed for asthma, targeting airway inflammation and relaxation of airway smooth muscle. As our understanding of asthma pathogenesis evolves, new drugs are being developed to manage a disease that affects 24 million Americans and 334 million worldwide.

DRUG DEVELOPMENT

A drug undergoes several phases of development until it is marketed (Fig. 22.1) (1). New drugs are initially developed based on our understanding of the essential biologic processes in disease pathogenesis based on human studies and animal models of human disease. One approach to develop a drug is to model a critical step of a pathway in an *in vitro* system (e.g., biologic response to a cytokine receptor) and test several compounds to identify those that affect the pathway. Pharmaceutic industries have libraries with thousands of natural and synthetic chemicals, peptides, nucleic acids, and other organic molecules which can be screened in high-throughput assay systems to test their biologic activity. Another approach is to design new compounds based on crystallography three-dimensional structure of the target molecule (e.g., a receptor) and computer-design and synthetize a drug, atom by atom, creating a three-dimensional

molecule that will interact with the target (e.g., disrupt ligand-receptor binding). These designed drugs are then tested in biologic systems for their activities. A third approach is to use biotechnology to produce recombinant molecules that act as agonists (e.g., a cytokine) or antagonists (e.g., monoclonal antibodies, soluble receptors) in the targeted pathway. In the case of monoclonal antibodies, they were initially produced in mouse cell systems, but later biotechnologic advances allowed humanization of these antibodies by changing murine immunoglobin G (IgG) antibody protein sequences to human IgG sequences except for the principal amino acids responsible for binding to the target epitope (10% murine and 90% human amino acid sequence). This humanization of the antibody minimizes immunogenicity while sparing specificity and biologic activity (e.g., omalizumab [anti-IgE], mepolizumab and reslizumab [anti-IL-5], lebrikizumab [anti-IL13], and benralizumab [anti-IL5 receptor α]) (2–4). More recently, human cell hybridoma systems have allowed direct production of fully human monoclonal antibodies for therapeutic use (e.g., dupilumab [anti-IL-4 receptor α]) (4). Besides antibodies, biotechnology has produced recombinant human molecules for asthma trials, such as interleukin (IL) 4 soluble receptor (5), interferon γ (6), IL-12 (7), and others (4). Newer approaches to develop biologic treatments include genetic alteration of animals to produce human molecules (e.g., making goats secrete human growth hormone in their milk), DNA-based therapies (8), virus vectors for human gene therapy, epigenetic tools (e.g., small interfering RNAs) (9), stem cell (10), and genome-editing technologies (e.g., using CRISPR/Cas9) (11).

A drug is usually developed together with several chemically similar counterparts. These similar compounds are tested in biologic systems *in vitro* and in animal models of human disease for their biologic activities to eventually identify a single or a few compound(s) for further development. These compounds may undergo chemical modifications to improve their eventual clinical application based on extensive understanding of the organic chemical characteristics necessary for resistance to gastrointestinal digestion and successful oral absorption (bioavailability), to prolong half-life by affecting distribution and metabolism, and to avoid toxicity. After *in vitro* testing, the drug is tested in animals for bioavailability, biologic activity, specificity of action, and toxicity. After a lead compound is selected, the pharmaceutic company files for a patent to obtain exclusive rights to market it for 20 years. Next, the drug enters the preclinical phase of development to establish an extensive safety profile of the drug in standard animal and cell culture systems. This phase includes *in vitro* and animal experiments to assess dose range, lethal dose 50% (dose that kills

50% of exposed animals), acute and chronic toxicity, teratogenesis, mutagenesis, carcinogenesis, effects on pregnancy, and so on. During this phase, the pharmaceutic company discusses with the FDA about safety data in animals that will be required to start human studies. Once these requirements are fulfilled, the pharmaceutic company works closely with the FDA to design the first human study with the new drug, aiming at assessing PK in humans. This study is submitted to the FDA as an Investigational New Drug (IND) application. Only after the FDA approval, the IND can begin the first clinical trial, initiating the clinical phase (human studies) of drug development.
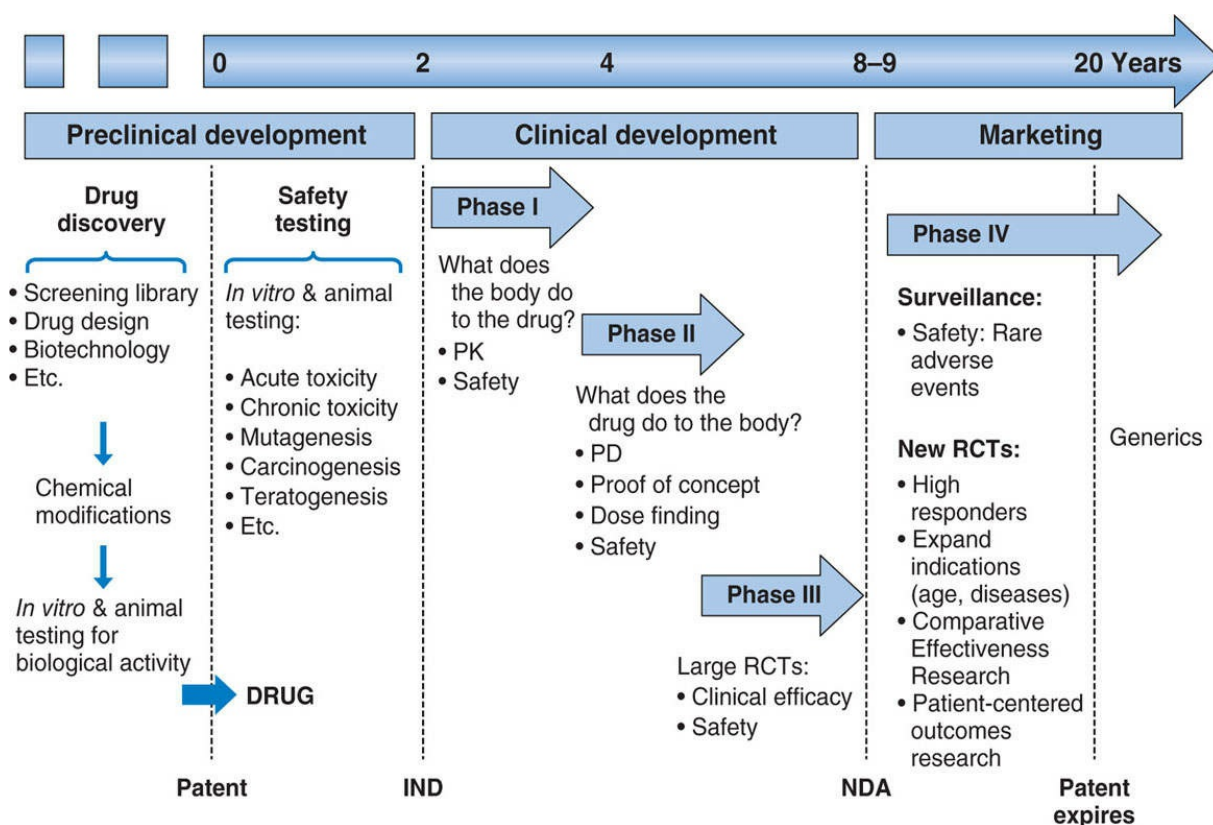
■ **FIGURE 22.1** Phases of drug development. IND, Investigational New Drug approval; NDA, New Drug Application approval; PD, pharmacodynamics; PK, pharmacokinetics; RCTs, randomized clinical trials.

The clinical development of a drug to attain FDA approval for marketing involves three phases of clinical studies. All studies in these phases are designed by the pharmaceutic company with continuous discussions and oversight from the FDA. In phase I studies, the drug is administered to few humans (e.g., $n = 10$) for the first time after completion of preclinical safety studies. The main aim of phase I studies is to understand drug's PK, determining the maximum tolerated dose, time to peak serum level, bioavailability, half-life, metabolism, volume distribution, and route of elimination. Secondary aims include initial

safety assessment (adverse effects) and measuring biomarkers of drug activity.

Based on the dose that worked in animal studies and on PK data in humans, phase II studies are designed to assess PD, that is, to determine whether the drug causes the expected biologic effects for the targeted human disease. Two kinds of studies are usually conducted in this phase: proof-of-concept and dose-finding studies. In proof-of-concept studies, the biologic effect of the drug on the disease of interest is assessed in small randomized clinical trials where usually the maximal tolerated dose is administered to determine whether the new drug has the expected biologic activity in humans. In asthma, a common proof-of-concept study is to assess the inhibitory effect of the drug on the early airway response (EAR) and late airway response (LAR) to inhaled allergen challenge. Often, pharmaceutic companies conduct a couple of proof-of-concept studies that are considered "go" or "no-go" trials; that is, depending on the presence or absence of signs of biologic activity, the drug will or will not proceed in further clinical development, respectively. In a dose-finding trial, a few hundred subjects are randomized to placebo or two or more different dose regimens in a double-blind manner to determine what doses improve disease-related outcomes (e.g., forced expiratory volume in 1 second [FEV_1] in asthma). Surrogate biologic markers of efficacy are often used to enable these trials to be short and thus less costly. Such secondary outcomes may include assays in patients' samples to determine whether the drug had the expected biologic effects in the targeted pathway. For example, in trials of omalizumab, a neutralizing anti-IgE antibody, besides asthma clinical outcomes, serum-free IgE concentration was also measured as a surrogate marker of drug efficacy, which was achieved when free IgE was lowered to undetectable levels. At the end of phase II trials, researchers know the dose that affects important disease physiologic outcomes and have additional safety data in hundreds of individuals. This information is then used to plan and design phase III clinical trials to assess clinical efficacy and to obtain additional safety data to apply for FDA approval to market the drug.

Phase III studies are large double-blind, placebo-controlled, randomized clinical trials designed to determine whether the drug improves clinically relevant outcomes selected by the pharmaceutic company and FDA. For asthma, some of the main outcomes to establish efficacy are airway obstruction (pulmonary function test), symptoms, quality of life (QOL) and frequency of exacerbations (see Table 22.1). The FDA usually requires more than one phase III trial demonstrating efficacy. If phase III trials are successful, the pharmaceutic company submits to the FDA a New Drug Application (NDA) to obtain approval for marketing. This application contains all data available on the

drug since its preclinical development, as well as data from clinical studies in 3,000 to 5,000 patients. The FDA takes on average 6 months to approve or deny an NDA (range: 3 months to years) and may seek input from outside experts. Once approved, the pharmaceutic company can market the drug with exclusivity until the patent expires, at which point other companies can start producing and marketing the drug without having to pay a fee to the patent holder. After approval, new phase III studies can be undertaken to expand indications to different age groups (e.g., pediatrics) and new diseases, which can help extend duration of patents.

After FDA approval, phase IV studies are designed to monitor safety aiming at identifying severe and rare side effects, such as those occurring at a rate of 1:10,000 or rarer. Examples of rare adverse events discovered in this phase include liver toxicity caused by telithromycin, cardiovascular events caused by rofecoxib, progressive multifocal leukoencephalopathy caused by JC virus in those receiving rituxan (anti-CD20), tendon rupture in patients taking quinolones, and, possibly, increased risk of asthma-related death in patients taking long-acting bronchodilators, particularly in African Americans not taking inhaled corticosteroids (ICSs). Besides phase IV trials, these rare serious events can be captured through the FDA surveillance system for medications' adverse events called MedWatch (http://www.fda.gov/safety/medwatch/default.htm), which allows health care professionals to report adverse events directly to the FDA online. Rare serious adverse events related to a drug lead to "black box warnings" in the drug's package insert, limitations of FDA–approved indications based on new risk and benefit ratio assessments, and even drug withdrawal from the market.

The costly development of new drugs is a risky business. It is estimated that the cost to bring a new drug to market can reach over $1.5 billion. Many drugs fail during clinical development, and only 30% of marketed drugs return the costs for their development. New drugs can fail even after marketing in phase IV studies because of rare life-threatening adverse events, leading to restrictions in use or withdrawal from the market. Although patent protects marketing of new drugs for 20 years, it usually takes 8 to 10 years to obtain FDA approval to market a drug, leaving 10 or fewer years for the pharmaceutic company to profit from a drug. This profit should not only cover the expenses incurred to develop the drug itself but it should also fund research and development of new drugs to keep the pharmaceutic company in business. Successful drugs can be highly profitable such as atorvastatin (Lipitor) with over $12 billion in annual sales during 2005 to 2008, or fluticasone-salmeterol inhaler (Advair) with almost $8

billion in sales in 2008 and over $4 billion annually from 2011 to 2013, omalizumab (Xolair) over $1 billion annually from 2011 to 2014 and over $2 billion in 2015, and adalimumab (Humira) $14 billion in 2015.

TABLE 22.1 OUTCOMES IN ASTHMA CLINICAL TRIALS

MEASUREMENT	PROCEDURE REQUIRED	ASTHMA COMPONENT ASSESSED
Allergy to airborne allergens	Allergy skin testing or specific serum IgE	Atopy or IgE sensitization
FEV_1 or FEV_1/FVC ratio	Spirometry	Airway obstruction
Post-bronchodilator FEV_1	Spirometry pre– and post–short-acting bronchodilator	Reversible bronchospasm component
Best achievable FEV_1 or FEV_1/FVC ratio	Spirometry after maximum asthma therapy for 1 wk	Possibly a measure of remodeling
Peak expiratory flow rate (PEFR)	Portable PEFR meter	Frequent monitoring of airway obstruction
Provocative concentration to decline FEV_1 by 20% (PC_{20})	Methacholine challenge	Airway hyperresponsiveness
Early and late airway responses to allergen	Whole lung inhalation allergen challenge	IgE-mediated response to allergen in lower airways
Lavage of allergen-challenged segmental bronchus	Bronchoscopy	Induction of Th2 inflammation in a segment of lower airways
Bronchial mucosal biopsy	Bronchoscopy	Airway inflammation and remodeling

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Sputum eosinophils	Sputum induction	Airway inflammation
Blood eosinophils	Blood draw	Airway inflammation
Fractional exhaled nitric oxide (FeNO)	Exhaling into NO analyzer	Airway inflammation
Exhaled breath condensate	Measure small molecular inflammatory markers and pH	Airway inflammation
Symptom diary	Complete diary forms	Symptoms
Asthma quality of life questionnaire	Complete questionnaire	Impact of asthma on own life (patient's perspective)
Asthma control questionnaire	Complete questionnaire	Ongoing severity of asthma (physician's perspective)
Asthma utilization	Complete questionnaire	Asthma impact on school/work and social activities

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobin E; NO, nitric oxide.

POSTMARKETING TRIALS

After FDA approval to market a drug, postmarketing studies (phase IV trials) may be undertaken for a variety of purposes. If adverse events are a concern, the FDA may mandate additional monitoring of specific adverse events. For example, studies of safety of long-acting β agonist (LABA) inhalers (12), and the EXCELS study which thus far has shown no increase in risk of cancer in patients receiving omalizumab for asthma (13), although omalizumab may increase risk for arterial thromboembolic events (14). Additional phase IV clinical trials can also be designed to compare efficacy and safety of the new drug with those of existing drugs, to determine the best step therapy to use the new drug, and to evaluate safety and efficacy in children or in other disease

indications. Moreover, analyses of combined data from multiple trials and new stratified trials can identify and prospectively validate biomarkers and clinical features that characterize best responders to the new drug, allowing personalized asthma care (15–17).

These aforementioned phase IV clinical trials are efficacy trials where carefully selected patients are enrolled, close monitoring ensure high treatment compliance, and several outcomes are frequently measured. Another category of postmarketing studies is effectiveness trials where performance of a treatment is compared to a control treatment in the real world, generally in primary care clinics. In these trials, inclusion and exclusion criteria are less stringent, study visits minimized, and few clinically relevant outcomes measured.

Another category of trials is patient-centered outcomes research trials where multilevel interventions with known efficacious treatments are compared in the community, at home, or in health care system setting to optimize implementation of management guidelines. Intervention involves education of patients, family, physicians (e.g., primary care doctors, emergency department doctors) as well as community agencies that can undertake home visits to teach home disease management, and/or to identify and reduce exposure to potential home environmental disease exacerbators (18).

OUTCOMES IN ASTHMA TRIALS

Outcomes measured in asthma trials have evolved as has our knowledge on asthma pathogenesis, clinical trial design, and technology to measure biomarkers. In the early 1900s, pathologic and clinical evidence already indicated that asthma pathogenesis involved bronchoconstriction, eosinophilic bronchitis, and natural allergen exposure triggering asthma and hay fever symptoms. The advent of pulmonary function testing in the 1940s to 1950s led to demonstration of reversible airway obstruction and airway hyperresponsiveness in patients with asthma. In the 1970s, inhalation allergen challenges allowed the experimental observation of early and late airway bronchospastic responses associated with increased blood eosinophilia. In the 1980s, bronchoscopic biopsies of bronchial mucosa revealed chronic airway inflammation even in patients with mild disease, which is characterized mainly by eosinophilic bronchitis, and increased CD4$^+$ T cells. In the 1990s, remodeling was described, which entails alterations in the resident structural cells resulting from chronic airway inflammation driven by infiltrating leukocytes. Remodeling includes goblet cell hyperplasia, smooth muscle cell hyperplasia, collagen

deposition in the subepithelial reticular membrane, increased innervation and vasculature, among other changes (19). Currently, research continues to focus on mechanisms of inflammation, heterogeneity of airway inflammation (endotypes of asthma), innate response, interactions between resident cells and leukocytes, and inflammatory changes during asthma exacerbations which are mainly triggered by respiratory viral infections.

The number and variety of clinical outcomes measured in asthma trials expanded based on our understanding of pathogenesis of airway disease as aforementioned (20). Pulmonary function tests (21) assess airway physiology such as spirometry to measure FEV_1 to evaluate changes in airway flows, a function of airway caliber. Portable peak expiratory flow (PEF) meters allow patients to monitor airway flow at home. More recently, electronic portable devices can measure and record PEF, FEV_1, and forced vital capacity (FVC) of 6 seconds, greatly expanding our ability to monitor variability in airway obstruction, a hallmark of asthma.

Airway hyperresponsiveness to nonspecific stimuli is also measured in asthma trials because it is an important feature of asthma (22,23) and because it correlates with airway inflammation. It is commonly measured as the provocative concentration of methacholine or histamine to cause a 20% decline in FEV_1 (PC_{20}). Airways of individuals with asthma undergo excessive bronchoconstriction upon inhalation of methacholine or histamine, which act directly on smooth muscles causing contraction. Airway hyperactivity is defined as a PC_{20} < 8 mg/mL for these two direct agents (24). ICS therapy simultaneously improves both hyperresponsiveness and airway inflammation. Indirect agents are used less often to assess PC_{20}. They cause bronchoconstriction indirectly by stimulating mast cells to release bronchospastic mediators, including histamine, cysteinyl leukotrienes, and prostaglandin D_2. Examples of indirect agents to assess airway responsiveness include exercise, inhalation of adenosine, or inhalation of osmotic stimulants, such as cold dry air, distilled water, hypertonic saline, or mannitol (25). PC_{20} using indirect agents can correlate more closely with airway inflammation than PC_{20} using direct agents (methacholine and histamine). Airway hyperresponsiveness can also occur in medical conditions other than asthma, including allergic rhinitis without asthma, up to 6 weeks after respiratory virus infections, and in smokers with chronic obstructive pulmonary disease (24) (see Table 19.3).

The realization that IgE sensitization and inhalation of a relevant allergen causes reproducible **EAR and LAR** led to the development of a widely used proof-of-concept asthma study model. In this model, subjects inhale increasing amounts of allergen—to which they react in allergy skin testing—to determine the concentration of allergen that causes a 20% decline in FEV_1. Then, the subject receives placebo and/or drug therapy for a period of time and returns for a repeat allergen challenge using the same allergen and dose as the initial challenge to determine whether the drug attenuates airway responses to the allergen. Because EAR and LAR are very reproducible, only 10 to 12 patients are needed per group to assess whether a drug attenuates any response by 30% or more. Almost all currently available asthma drugs attenuate EAR or LAR or both (2,3,26–41), making this study model a common phase II trial to determine whether a new drug works for asthma (Fig. 22.2). Drugs that inhibit mast cell activation and bronchoconstriction should attenuate EAR, whereas drugs that inhibit delayed production of mediators or airway influx or function of leukocytes (e.g., eosinophils, dendritic cells, and lymphocytes) can inhibit LAR. This model of inhalation allergen challenge that induces 20% decline in FEV_1 also increases airway hyperresponsiveness and sputum eosinophilia 24 hours after the challenge, allowing researchers to assess the effects of new drugs in these outcomes as well. The presence of LAR seems to be driven by T cells because studies of peptide immunotherapy revealed isolated late-phase reactions to injections without acute reactions (42). Peptides are too small to cross-link IgE and stimulate mast cells, but they do bind to human leukocyte antigens and stimulate T cells. Lastly, EAR and LAR responses in the lower airways are not unique to patients with asthma. They can also be present in nonasthmatic allergic rhinitic patients after rhinovirus colds (43), raising the hypothesis that a spectrum of disease progression in the lower airways may occur, such as IgE sensitization, bronchial hyperresponsiveness, bronchial EAR and LAR to allergen challenge, and finally full-blown asthma.
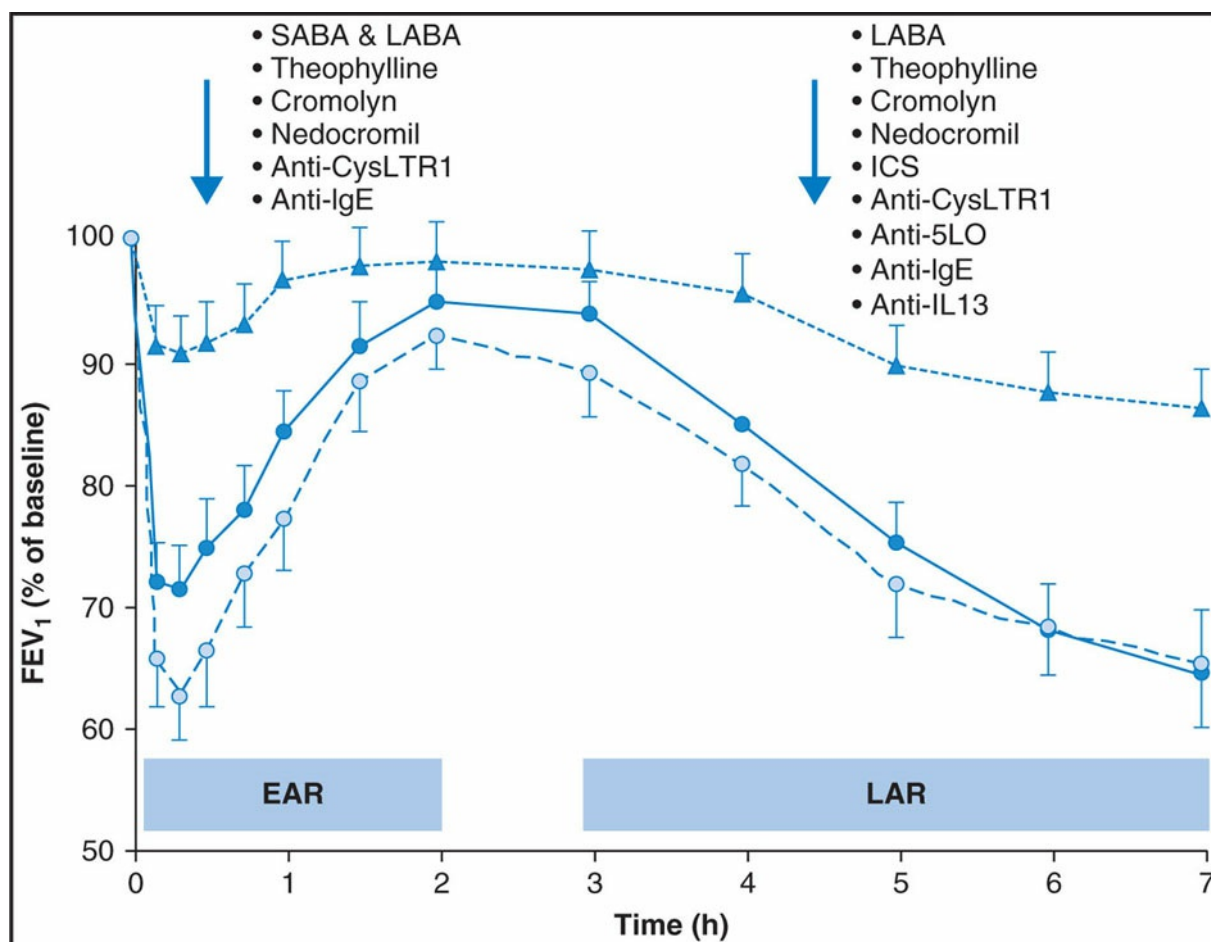
FIGURE 22.2 Inhalation allergen challenge causing biphasic airway response in patients with asthma. Graph showing percentage changes in mean FEV_1 and SEM from baseline to 7 hours postchallenge. Changes are reproducible between inhalation challenges performed 4 weeks apart (traced and continuous lines). Bronchoconstriction occurs within minutes and improves in 2 hours (EAR) mostly as a consequence of smooth cell contraction. Then, 3 to 8 hours after challenge, bronchoconstriction recurs as a consequence of increased influx of leukocytes, particularly eosinophils, Th2 lymphocytes, and basophils (LAR). Listed are medications that inhibit EAR and LAR (*top line*) when administered before the challenge. Anti-IL5 antibodies (mepolizumab and reslizumab) do not alter EAR or LAR. The effects of dupilumab and of long-acting muscarinic antagonists (LAMA) on allergen airway responses in humans have not been published. FEV_1, forced expiratory volume in 1 second; EAR, early airway response; LAR, late airway response; anti-CysLTR1, antagonists of cysteinyl leukotriene receptor 1 (e.g., montelukast, zafirlukast); anti-5LO, antagonist of 5-lipoxygenase (e.g., zileuton); anti-IgE, antibody anti-IgE (e.g., omalizumab); ICSs, inhaled corticosteroids; LABA, long-acting β_2 receptor agonist bronchodilators (e.g., salmeterol, formoterol); SABA, short-acting β_2 receptor

agonist bronchodilators (e.g., albuterol, terbutaline).

Another common proof-of-concept study design used in phase II trials to assess efficacy of new asthma controllers rather than acute relievers of bronchospasm, is the **corticosteroid withdrawal model**. In this model, subjects with moderate-to-severe asthma enter a run-in period on inhaled plus or minus oral corticosteroid therapy that is (are) titrated to the minimum corticosteroid dose necessary to control symptoms, at which point subjects are randomized to placebo or the new drug as an add-on therapy. Then, after a period on corticosteroid therapy and study medication (either new drug or placebo), corticosteroid therapy is tapered to determine whether the new drug is more efficacious than placebo in maintaining asthma control. In this kind of study, patients need to be monitored very closely, and protocols for action plan need to be in place to rescue patients when their asthma deteriorates. The corticosteroid withdrawal study is a model of loss of asthma control caused by worsening airway inflammation. It is not a model to study asthma exacerbations because acute exacerbations are caused by common colds in up to 80% of the episodes (44,45). Exacerbations occur when virus-induced inflammation superimposes to chronic allergen–driven inflammation. **Studies evaluating asthma exacerbations** recruit patients who have exacerbated in the previous year and follow them for a long period (e.g., 12 months) to capture new episodes of acute asthma deterioration requiring a short course of systemic corticosteroid therapy. Asthma exacerbation rate has increasingly become a primary outcome in asthma clinical trials evaluating new drugs because current available therapies are very efficacious in controlling symptoms, airway function, QOL, and other asthma outcomes.

The recognition that asthma is a chronic inflammatory airway disease led to implementation of **measurements of inflammation** in clinical trials (see Table 22.1) (46). Blood eosinophilia is a marker to select patients with allergic inflammation for biologic therapies targeting eosinophils and Th2 inflammation. Bronchoalveolar lavage and bronchial mucosal biopsy reliably assess luminal and tissue inflammatory infiltrates, but necessitate bronchoscopy which precludes their use in large clinical trials. In the 1990s, sputum induction using hypertonic saline solution started to be used in asthma studies as a noninvasive technique to assess lower airway inflammation, but it remains a research tool. Sputum eosinophilia (>2% of nonsquamous cells) is characteristic of allergic asthma, increases after allergen challenge (47) and decreases with therapy, including systemic (48) or ICS (49), leukotriene antagonists, (50) and biologic immunomodulators targeting mediators of allergic inflammation, (4) such as IgE

(omalizumab) (51–53), IL-5 (mepolizumab (54–56) and reslizumab (57,58)), and IL-5 receptor α subunit (benralizumab) (59,60). Biologicals targeting IL-5 reduce blood and sputum eosinophils and are efficacious in patients with asthma and eosinophilia (61). Anti-IL-13 antibodies (e.g., lebrikizumab and tralokinumab) can increase blood eosinophil count (62) and have had modest clinical efficacy in asthma trials (63,64). An anti-IL-4 receptor α (dupilumab) may also increase blood and sputum eosinophilia (65), but improves asthma outcomes (66). Mast cell stabilizers (cromolyn and nedocromil) improve symptoms of asthma and airway function, but have mild and inconsistent anti-inflammatory effects as measured by eosinophil count or eosinophil products in airways and blood (67–70). It is noteworthy that sputum eosinophilia is not pathognomonic of asthma and can also occur in patients with eosinophilic bronchitis or chronic eosinophilic pneumonia. In addition, sputum neutrophilia, not eosinophilia, can be found in some patients with asthma, particularly those with nonatopic or more severe disease (71–73).

Because of the risk of severe bronchospasm with inhalation allergen challenge, other models have been developed to study the effects of drugs in allergic airway inflammation. In one model, allergen is infused into a bronchial tree segment to induce localized airway allergic inflammation, the so-called **segmental allergen challenge model** (74). An equal amount of saline is infused in another segmental bronchus in the contralateral lung as a control challenge. Subsequent bronchoscopies are then performed to collect bronchoalveolar lavages of the same segments to evaluate early and late local inflammatory responses. Yet another model to induce mild airway inflammation of lower airways is the **repeated low-dose inhalation allergen challenge model** (75,76), in which subjects inhale the allergen dose calculated to cause only 5% decline in FEV_1, based on a baseline allergen challenge. The same dose is inhaled daily for 5 or more days to induce airway eosinophilia, worsen hyperresponsiveness, and to cause none-to-mild short-living asthma symptoms, thus reproducing many features of asthma while avoiding the risk of severe bronchoconstriction associated with high-dose inhalation allergen challenges to induce EAR and LAR. Both the segmental and the repeated low-dose allergen challenge models are not widely used owing to the need for bronchoscopy and labor. Bronchoscopy with mucosal biopsy, however, has been used in clinical trials to assess the effect of therapy on airway inflammation (51) and remodeling (e.g., subepithelial collagen deposition (77,78)).

An approach to indirectly **measure airway remodeling** is to administer a short course of maximal therapy. Because it is not practical to perform

bronchoscopy for mucosal biopsy to histologically measure remodeling in large trials, researchers have used a short course of maximal therapy to reduce inflammation and bronchospasm and measure "the best achievable" FEV_1 (79). In this study model, before and after an intervention, patients undergo a week of oral corticosteroid, maximal dose of ICS–long-acting bronchodilator (ICS + LABA) combination and a leukotriene antagonist treatment. At the end of the week of maximal asthma therapy, FEV_1 is measured before and after maximal bronchodilation with administration short-acting bronchodilator (short-acting β_2 agonists [SABA]). This best achievable FEV_1 is considered by some to be a measurement of remodeling, which is assumed to be the irreversible component of airway obstruction after maximal therapy to reverse bronchospasm and to improve any reversible component of bronchial inflammation. However, this assumption has not been validated by comparing best achievable FEV_1 (or FEV_1/FVC ratio) with bronchial biopsy measures of remodeling (e.g., goblet and gland cell volume, smooth muscle volume, and subepithelial reticular membrane thickening).

Noninvasive **measurements of airway inflammation** were developed in the 1990s and 2000s and include fractional exhaled nitric oxide (FeNO) and EBC. Nitric oxide (NO) can be measured as a gas in exhaled air. It is produced by the action of nitric oxide synthases (NOS) on L-arginine. In the lungs, NOS are found in airway epithelial and endothelial cells. Airway epithelial cells express inducible NOS (aka iNOS or NOS_2) upon stimulation by several inflammatory pathways, including interferons (via signal transducer and activator of transcription [STAT]-1), Toll-like receptors (via nuclear factor kappa B), and IL-4 (via STAT-6) which are activated both in respiratory infections and allergic inflammation. NO has several roles, including vasodilation, bronchodilation, and innate defense by inflicting nitrosative distress via nitration, nitrosation, and nitrosylation of molecules. Guidelines have been devised on how to measure FeNO because several factors can alter its concentration, such as food intake, contamination with upper airway NO, air flow, and other diseases besides asthma (80). Normal levels are <25 parts per billion (ppb) (or <10 ppb for children <12 years of age), and untreated atopic patients with asthma usually have levels >50 ppb (or >35 ppb for children). Intermediary levels are not indicative of asthma. As with sputum eosinophilia, FeNO correlates with more severe disease, degree of allergic airway inflammation, and decreases promptly with ICS therapy. FeNO can be elevated in other conditions, such as acute respiratory viral infections, bronchiectasis, alveolitis, chronic bronchitis, cystic

fibrosis exacerbation, atopic individuals, (e.g., allergic rhinitis), chronic cough, and pneumonia. FeNO decreases in systemic or pulmonary hypertension, heart failure, smokers, and after caffeine intake. FeNO can be helpful, particularly in atopic patients with asthma, to monitor the need to increase ICS therapy or to improve patient compliance (81), although this is still controversial (82,83).

Another noninvasive measure of airway inflammation is EBC. It is collected by having the patient breathe out through a cooled tube where water vapor from exhaled breath condensates and accumulates. Guidelines have been established for its collection as well (84). EBC contains low-molecular-weight compounds such as inflammatory mediators, including chemokines, cytokines (e.g., IL-8, IL-6), prostaglandins, thromboxanes, leukotrienes, 8-isoprostane, and markers of oxidative and nitrosative stress. EBC pH can also be measured, and it lowers during asthma exacerbations (85). Analysis of EBC is currently a research tool, but has the future potential to aid in diagnosing asthma, asthma exacerbation, gastroesophageal reflux (86), and in monitoring airway inflammation. Potential future biomarkers that could become useful to select patients for treatments and to monitor treatment response include metabolites in body fluids (serum, urine, and EBC) (87) and imaging of lung airways and ventilation defects (88). Besides new measurements to assess disease pathogenesis, new tools have been developed to assess clinical improvement in trials, namely, **quality of life (QOL)** and asthma control questionnaires. QOL questionnaires are patient centered and aim at assessing how disease severity affects patients from the patient's perspective (89). They are developed by asking patients with the disease of interest how the disease affects them in terms of the most bothersome symptoms, limitations on daily activities specifically caused by the disease, and emotional consequences resulting from disease severity. The QOL is summarized into one score, and the minimal clinical important difference determined. Several QOL questionnaires specifically developed to assess the impact of asthma in patients' lives have been validated; that is, changes in QOL scores correlated well with changes in traditional asthma outcome variables (90,91). Several patient-centered QOL instruments have been developed for asthma, respiratory diseases, (92) and several other diseases (93).

Another type of tool, the **asthma control questionnaire**, was developed to assess disease severity from the physician's perspective (94). Experts in asthma were asked which variables were the most important to ensure that asthma is well controlled and minimally impacting the patients' lives. A few variables considered the most important to assess control based on the majority of the experts were included in the tool and validated in trials. There are a few

validated asthma control tools that usually contain questions about frequency of daytime and nocturnal symptoms, limitation of activities because of asthma, and use of rescue bronchodilator. Asthma QOL tools and asthma control tools have joined the traditional symptom diary as measures of clinical severity of asthma in trials. Additional variables used in clinical trials are asthma-free days and exacerbations. **Asthma-free day** is defined as a day in which symptoms, asthma impact on patient's life and use of rescue medication were minimal or nonexistent. **Asthma exacerbations** have been defined as aggravation of symptoms associated with moderate worsening in airway obstruction, but nowadays it is more commonly defined as deterioration of asthma necessitating systemic steroid therapy or unscheduled physician's visit, a more clinically relevant definition and rarer event (95). Tools have also been developed to quantify utilization of health care for asthma in trials (e.g., emergency department visits, hospitalizations) (96).

Current clinical trials assess several outcomes to ensure that a drug or an intervention benefits the hallmark components of asthma, such as symptoms, airway obstruction, airway hyperresponsiveness, and airway inflammation. Symptoms are appraised with symptom diary, and periodic assessments of asthma QOL and asthma control. Airway obstruction is monitored twice daily via PEF measurements and at study visits with spirometry. Airway hyperresponsiveness is assessed through methacholine inhalation challenges and airway inflammation monitored with FeNO and/or sputum eosinophil measurements. No single measurement can assess all hallmark components of asthma. It is reassuring when a therapy consistently improves all of these measurements in clinical trials.

ASTHMA CLINICAL TRIALS

Over 10,000 clinical trials have been conducted to assess treatments in patients with asthma since 1960s. The sources for information on ongoing clinical trials and on published and unpublished completed trials are listed in Table 22.2. Table 22.3 lists the results of important clinical trials conducted in patients with asthma. These clinical trials and many others have shaped the recommendations in national and international Asthma Guidelines (97,98).

Asthma clinical trials have assessed many medications for asthma treatment over the years. Some of the first clinical trials in patients with asthma evaluated the efficacy of inhaled short-acting bronchodilators (SABA and anticholinergic drug) (99,100) and oral corticosteroids for acute deterioration of asthma

(101–103), which have remained the mainstay of therapy for asthma exacerbations for over 40 years. Addition of inhaled anticholinergic drug can reduce admissions from the emergency department in children (100), and high-dose ICS decreases risk of relapse of exacerbation symptoms within a month (104).

For chronic asthma control, several drugs have been developed, including oral methylxanthines (e.g., theophylline, aminophylline), inhaled cromolyn, ICS, inhaled nedocromil, inhaled LABA, oral leukotriene antagonists, inhaled long-acting muscarinic receptor antagonists (LAMA), and parenteral biologic immunomodulators, such as antibodies against IgE, IL-5, IL-4 receptor α, and IL-5 receptor. The realization that asthma is a chronic airway inflammatory disease (105) led to the use of ICS for chronic asthma therapy which remains the most efficacious therapy and reduces asthma mortality (97,106). Even for those with mild asthma, daily ICS is superior to daily SABA in reducing symptoms and improving lung function (107,108). In addition, the BAGS (Beta AGoniSt for mild asthma) study (109) showed that regular use of SABA four times a day was not superior to SABA used as needed, and therefore, SABA should be used as needed. Regular daily SABA use can be deleterious for patients with asthma homozygous for genotype Arg/Arg in the 16th amino acid of the β_2-adrenergic receptor gene (see BARGE trial in Table 22.3), an effect not observed with LABA (LARGE trial, Table 22.3).

TABLE 22.2 SOURCES OF INFORMATION ON ASTHMA CLINICAL TRIALS

DATABASE	TYPES OF TRIALS	INTERNET URL
NCBI PubMed Europe PMC	Published articles describing clinical trials.	https://www.ncbi.nlm.nih.gov/pubmed https://europepmc.org
Cochrane Library Clinical Evidence	Meta-analyses and systematic reviews of published and unpublished asthma trials.	http://www.cochrane.org http://clinicalevidence.bmj.com
ClinicalTrials.gov European Union Clinical Trials Register	Registries of governmental and privately supported	https://www.clinicaltrials.gov https://www.clinicaltrialsregister.eu

	clinical trials, both completed and ongoing trials.	
FDA EMA	Regulatory agencies that approve marketing of drugs. Industry's filing documents may be posted online.	https://www.fda.gov http://www.ema.europa.eu

EMA, European Medicines Agency; FDA, US Food and Drug Administration; NCBI, National Center for Biotechnology Information.

For patients with asthma not well controlled on low-dose ICS, numerous trials have shown that adding LABA is more beneficial than increasing ICS (FACET trial, Table 22.3). LABA controls symptoms well, but has no significant anti-inflammatory effect. In patients well controlled on ICS alone or on ICS + LABA, ICS cannot be stopped, and patients switched to LABA monotherapy because their airway inflammation worsens despite good symptom control, putting them at increased risk for treatment failures and asthma exacerbations as demonstrated in the SOCS (Salmeterol Or CorticoSteroids) (110) and SLIC (SaLmeterol + Inhaled Corticosteroids) (111) trials. For patients with asthma not controlled on ICS, adding LABA improves symptom control, whereas increasing ICS improves airway inflammation and reduces risk for exacerbations. Interestingly, stepwise escalation of ICS dose with LABA achieves complete control in only 43% of patients with asthma as shown in the GOAL (Gaining Optimal Asthma control) study (112).

Patients tend to reduce use of controller inhalers once symptoms are well controlled. The IMPACT study (Table 22.3) showed that patients with mild persistent asthma can be fairly well controlled with as needed instead of daily ICS therapy. Reliever therapy has been based on short-acting bronchodilators because of their onset of action beginning in 5 minutes, but symptoms can worsen from increased airway inflammation that is not treated. Studies have repeatedly shown that reliever inhaler combination ICS + SABA (or ICS + LABA) to be superior to reliever therapy with SABA alone (BEST, SMART [O'Byrne], TREXA, and BARGE (113), see Table 22.3). This concept resulted in concerns about LABA safety, particularly after the SMART (Salmeterol Multicenter Asthma Research Trial) (114) showed a 4.3-fold increase in risk of death in patients who added salmeterol to their asthma therapy compared to

adding placebo. Post hoc data analysis revealed that this deleterious effect was observed largely in African Americans, in those not on ICS controller and in those without a primary doctor, leading to the hypothesis that the results might have been driven by patients who used salmeterol alone as controller therapy. As a result, the FDA mandated LABA safety studies in over 50,000 patients, whose initial results have been reassuring (AUSTRI and VESTRI trials, Table 22.3). Post hoc analyses of clinical trials data have shown that African Americans benefit less than Whites from adding LABA to ICS therapy (115,116). LAMA is an efficacious additional add-on therapy for patients whose asthma is not controlled on ICS alone (TALC trial) or on ICS + LABA (PrimoTinA trial, see Table 22.3).

Biologic therapies with monoclonal antibodies provide additional benefit for those not fully controlled on high-dose ICS or ICS + LABA combination, particularly by reducing risk for asthma exacerbations in patients with Th2 airway inflammation. Currently, FDA–approved monoclonal antibodies for patients with asthma include anti-IgE (omalizumab) (52,117) and anti-IL-5 antibodies (mepolizumab (55,56) and reslizumab (58)). Promising results have been seen with anti-IL-5 receptor α (benralizumab) (60,118,119) and anti-IL-4 receptor α (dupilumab) (66), whereas anti-IL-13 antibodies (e.g., lebrikizumab (63,120) and tralokinumab (64)) have been surprisingly disappointing for asthma despite successful earlier trials (121,122).

TABLE 22.3 IMPORTANT CLINICAL TRIALS IN PATIENTS WITH ASTHMA

TRIAL (REF.)	AIM	POPULATION	INTERVENTIONS	RESULTS	CO
Pauwels et al. (129) FACET (Formoterol And Corticosteroids Establishing Therapy) 1997	To evaluate the effect of adding formoterol (For) to low and high doses of budesonide (Bud).	$N = 852$, 18–72 y old. • $FEV_1 \geq 50\%$. • ≥15% FEV_1 reversibility. • ICS ≤1,600 µg/d of Bud equivalent.	Randomized to four arms: • Bud 100 µg bid • Bud 100 µg + For 12 µg bid • Bud 400 µg bid • Bud 400 µg + For 12 µg bid • Duration: 12 mo.	Adding For better controlled symptoms and improved FEV_1 and AM PEF than four times Bud. Higher dose of Bud better protected against exacerbations than adding For.	Add to I con sym imp airv obs than ICS ICS prev exa

Malmstrom et al. (130) 1999	To compare efficacy of ICS (Beclomethasone [Bec]) versus LTA (Montelukast [Mon]) in asthma.	$N = 895$, 15–85 y old. • FEV$_1$ 50%–85%	Randomized to three arms: • Pbo • Mon 10 mg qd • Bec 200 µg bid Duration: 12 wk.	Bec > Mon > Pbo in improving FEV$_1$, symptoms, QOL, and reducing exacerbations.	Bec to N is b Pbo mo sev Hal sho var ind resp dru
CAMP (131) (Childhood Asthma Management Program research group) 2000	To compare long-term efficacy and safety of nedocromil (Ned) versus ICS therapy in childhood asthma.	$N = 1,041$, 5–12 y old. • Mild-to-moderate asthma	Randomized to three arms: • Pbo bid • Ned 8 mg bid • Bud 200 µg bid All used albuterol (Alb) prn. Duration: 4–6 y.	No significant change in postbronchodilator FEV$_1$. Bud > Ned > Pbo in providing greater benefits in symptoms, AHR, exacerbation rate, and rescue Alb use.	Bud to N is b Pbo ther chil asth dec gro cm yea
Pauwels et al. (132) START (Inhaled Steroid Treatment as Regular Therapy in early asthma study) 2003	To determine long-term benefit of early start of ICS therapy for asthma.	$N = 7,241$, 5–66 y old. • Asthma diagnosed within 1 y. • Reversibility of airway obstruction. • FEV$_1$ ≥ 60%.	• Bud 400 (200 if <11 y old) µg/d versus Pbo. Duration: 3 y.	Bud reduced in 46% risk of severe exacerbations. Bud slightly increased postbronchodilator FEV$_1$ by 0.88%. Bud reduced growth in children by 1.3 cm.	Bud the sev syst cor and asth in p asth rece
Israel et al. (133) BARGE (Beta-Adrenergic Response by Genotype) 2004	To determine whether subjects with asthma homozygous for arginine (Arg) or glycine (Gly) in the 16th amino	$N = 76$, 11–50 y old. • FEV$_1$ ≥ 70% • Daily need	Crossover design: • 16 wk of Alb 180 µg or Pbo qid. Duration: 16 wk for each treatment	Arg/Arg patients improved AM PEF, FEV$_1$, symptoms and reduced rescue Ipra use while off	Pati hom for 16th acic B2/ wor

Study	Objective	Population	Intervention	Results	Conclusion
(continued)	acid of the B2AR respond differently to Alb.	• Treated with SABA only.	for rescue phase. Alb therapy, but < 56 puffs/wk. Washout of 8 wk. Ipratropium (Ipra) prn.	of Alb. Gly/Gly patients did better on Alb than on Pbo.	whi... Alb... fou... day...
Morgan WJ et al. (134) 2004	To determine whether tailored allergen avoidance improves asthma in inner-city pediatric population.	$N = 937$, 5–11 y old. • Allergen skin test showing allergy to aeroallergens (dust, rat, mouse, cockroach, mold, pets).	Randomized to real versus mock intervention tailored to decrease allergen and tobacco exposure. Education and implementation. Duration: 2 y.	Real intervention successfully reduced amount of allergens in home dust samples. It also reduced symptoms, missed school days, and unscheduled doctor's visits for asthma.	Tailored environmental intervention to reduce exposure to allergens and tobacco in children with asthma improves symptoms and reduces exacerbations.
O'Byrne et al. (135). SMART (Symbicort MAintenance and Reliever Therapy) 2005	To determine whether Bud/For can be used as maintenance and rescue medications for asthma.	$N = 2,760$, 4–80 y old. • FEV_1 = 60%–100% • Receiving 200–1,000 µg ICS • ≥12% reversibility • Using SABA prn almost daily.	Randomized to three arms: • Bud/For 80/4.5 µg bid + Terbutaline (Ter) prn. • Bud 320 µg bid + Ter prn • Bud/For 80/4.5 µg bid + prn. Duration: 2 y.	Bud/For bid + prn reduced exacerbation risk by 45% and symptoms, and improved lung function compared with the other two groups.	Bud/For can be used as both maintenance and rescue medication. For is a fast-acting LABA, improving lung function within 5 min.
Boushey et al. (79) IMPACT	To evaluate daily versus prn ICS for	$N = 225$, 18–65 y old.	Randomized to three arms: • Pbo bid	Daily Bud better improved	It may be possible to treat mild

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Study	Objective	Population / Inclusion	Intervention	Results	Conclusion
(IMProving Asthma Control Trial) 2005	mild persistent asthma.	• $FEV_1 \geq 70\%$. • $\geq 12\%$ reversibility or $PC_{20} < 16$ mg/mL. • Mild persistent asthma in run-in phase.	(intermittent Bud). • Bud 200 µg bid • Zafirlukast (Zaf) 20 mg bid. All groups: prn Bud 800 µg bid for 10–14 d, or Prednisone for 5 d if asthma worsened. Duration: 12 mo.	baseline FEV_1, sputum eosinophils, PC_{20}, and FeNO than the other two treatments. QOL, symptoms and FEV_1 after 1 wk of maximal therapy did not differ among groups, suggesting no deterioration of remodeling.	persistent asthma with prn ICS. Although intermittent ICS controlled well QOL and symptoms, its ability to prevent severe exacerbations and deaths are unknown.
Guilbert et al. (136) PEAK (Prevention of Early Asthma in Kids) 2006	To determine whether ICS prevents asthma in high-risk young children.	$N = 285$, 2–3 y old. • Positive asthma predictive index (≥ 4 wheezing episodes + atopy markers).	Fluticasone (Flu) 88 µg or Pbo bid for 2 y, the 1 y of follow-up off study medication.	During the 2 y of treatment, Flu improved symptoms, reduced exacerbations and need for rescue medications. In the third year, there were no differences between groups.	Two years of ICS in young children at high risk to develop asthma did not prevent asthma. But ICS controlled well asthma-like symptoms.
Papi et al. (137) BEST (BEclomethasone plus Salbutamol [albuterol] Treatment) 2007	To determine whether rescue therapy with combined	$N = 455$, 18–65 y old. • $FEV_1 \geq 75\%$. • $\geq 12\%$	Randomized to four arms: • A: Pbo bid + prn rescue Bec/Alb 250/100 µg	Exacerbation rate was lower in group A than group B, but similar	Patients with mild persistent asthma can be treated with symptom-

	Alb + Bec is better than Alb alone in mild persistent asthma.	reversibility or $PC_{20} < 8$ mg/mL.	• B: Pbo bid + rescue Alb 100 µg prn • C: Bec 250 µg bid + rescue Alb 100 µg prn • D: Bec/Alb 250/100 µg bid + rescue Alb 100 µg prn Duration: 6 mo.	among groups A, C, and D. Group A received the lowest cumulative ICS dose over the 6 mo. Group A was consistently better in improving lung function, symptoms, and use of rescue inhaler.	driven ICS/SABA therapy prn instead of regular ICS daily therapy.
Cox et al. (138) AIR (Asthma Intervention Research trial) 2007	To determine the effect of bronchial thermoplasty (BT) on the control of moderate or severe persistent asthma.	$N = 112$, 18–65 y old. • Bec ≥ 200 µg + LABA per day. • FEV_1 60%–85%. • $PC_{20} < 8$ mg/mL. • Alb prn ≤ 4 puffs/d. • Worsening control after holding LABA.	Randomized to • Bronchial thermoplasty • Continued medical therapy. Duration: 12 mo.	BT reduced by 50% loss of control during 2-wk LABA holding periods at 3, 6, and 12 mo, and improved AM PEFR (~7.5%), AQLQ, ACQ, symptoms and need for rescue SABA use.	BT done in three bronchoscopy sessions can improve control of patients with moderate-to-severe asthma and AHR during step-down therapy. Small sample size to assess effect on exacerbations.
Sorkness et al. (139) PACT (Pediatric Asthma	To compare three controller regimens for	$N = 285$, 6–14 y old. • $FEV_1 ≥$	Controllers: Flu 100 µg, Sal 50 µg, Mon 5 mg/dose.	Flu and Flu/Sal provided better and	Flu bid and Flu/Sal best controlled asthma, but

Controller Trial) 2007	children with mild-to-moderate asthma.	80%. • PC_{20} < 12.5 mg/mL.	Randomized to three arms: • Flu bid • Flu/Sal qAM, Sal qPM • Mon qPM Duration: 48 wk.	comparable asthma control than Mon. Flu best improved lung function and FeNO.	Flu bid improved the most markers of airway inflammation.
Peters et al. (140) LOCSS (Leukotriene or Corticosteroid or Corticosteroid–Salmeterol) 2007	To determine whether patients with asthma well controlled on ICS bid can be stepped down to once-daily ICS + LABA or Mon.	$N = 500$, ≥6 y old. • Controlled on Flu 100 µg bid. • FEV_1 ≥ 80%. • PC_{20} < 12.5 mg/mL.	Randomized to three arms: • Continued Flu bid • Flu 100 µg + Sal 50 µg qPM. • Mon 5 or 10 mg qPM Duration: 16 wk.	Treatment failure rate was similar between Flu bid and Flu + Sal groups (20%), and worst in the Mon group (30%). Asthma-free days was similar among all three groups.	Stepping-down patients with well-controlled asthma on ICS bid to ICS + LABA qPM is better than to Mon qPM.
Bacharier et al. (141) AIMS (Acute Intervention for Management Strategies trial) 2008	To compare efficacy of episodic ICS versus Mon for intermittent wheezing in children.	$N = 238$, 1–5 y old. • Moderate-to-severe intermittent wheezing ≥2 times with RTI in past year. • Wheezing episodes necessitating urgent care or oral corticosteroid therapy.	Randomized to three arms of episodic treatments for RTI for 7 d: • Bud neb 1 mg bid. • Mon 4 mg. • Pbo. All groups could use Alb prn. Duration: 12 mo.	All three groups had same proportion of episode-free days, oral corticosteroids use, health utilization, QOL and growth. Bud and Mon reduced trouble breathing and interference in activities.	In preschoolers, intermittent Bud or Mon for RTI are effective to control trouble breathing and activity interference, particularly for kids with positive asthma predictive index (API).

Study	Objective	Population	Design	Results	Conclusion
Ducharme et al. (142) 2009	To determine whether high-dose inhaled Flu at onset of RTI reduces need for rescue oral corticosteroids in children with recurrent wheezing.	$N = 129$, 1–6 y old. • ≥3 wheezing episodes in the past triggered by RTI. • Needed oral corticosteroid for wheezing two times in previous 12 mo. • Children with allergic rhinitis were excluded.	Randomized to two arms of episodic treatments for RTI for 10 d: • Flu 750 µg bid. • Pbo bid. Duration: 12 mo.	Oral corticosteroids use was used in 8% of RTIs in the Flu group versus 18% in Pbo group. Children in the Flu grew 0.3 cm and 0.3 kg less than those in Pbo group.	Preemptive high-dose Flu at onset of RTI reduces need for rescue oral corticosteroid therapy in preschoolers with recurrent wheezing, but reduces slightly growth rate.
Wechsler et al. (143) LARGE (Long-Acting Beta Agonist Response by Genotype) 2009	To determine whether those with genotype Arg/Arg in the 16th amino acid of β_2-adrenergic receptor (16-B2AR) respond differently to LABA than those with genotype Gly/Gly.	$N = 87$, ≥18 y old. • $FEV_1 \geq 40\%$. • $PC_{20} < 8$ mg/mL off of ICS or ≤16 mg/mL on ICS. Or reversibility of FEV_1 after SABA ≥12%. • Arg/Arg or Gly/Gly genotype in 16-B2AR.	All patients received Bec 240 µg bid and Ipra prn and underwent a crossover study on Sal 50 µg bid or Pbo bid. Duration: 18 wk/treatment period. Washout of 8 wk.	Compared to Pbo, Sal increased AM PEFR by 5% in both groups. Sal reduced AHR in patients with Gly/Gly genotype, but not in those with Arg/Arg genotype.	Addition of LABA to medium-dose ICS improved lung function to the same extent in both 16-B2AR genotypes. Sal improved AHR only in those with Gly/Gly genotype.
Lemanske et al. (115) BADGER (Best ADd-on therapy Giving Effective	In children with uncontrolled asthma on low-dose ICS, what is the best step up:	$N = 182$, 6–17 y old. • Uncontrolled asthma on Flu 100 µg bid.	Randomized crossover design with three treatment periods of 16 wk each:	Composite outcome (exacerbation, asthma control days, FEV_1) was best with	Adding LABA is better than increasing ICS or adding LTA in children

Responses) 2010	ICS 2.5 times, add LABA or add LTA?	• FEV$_1 \geq$ 60%. • PC$_{20}$ < 12.5 mg/mL or 12% reversibility after SABA.	• Flu 250 µg bid (ICS 2.5 times) • Flu 100 µg + Sal 50 µg bid (ICS + LABA) • Flu 100 µg + 5 or 10 mg qd Mon (ICS + LTA)	ICS + LABA. Worse control at baseline predicted greater response to ICS + LABA. Whites responded best to ICS + LABA. Blacks responded the least to ICS + LTA.	whose asthma is not controlled on low-dose ICS. There is racial variability in drug responses.
Peters et al. (144) TALC (Tiotropium bromide as an ALternative to increased inhaled Corticosteroid) 2010	In patients with asthma not controlled on ICS, addition of Tio is superior to doubling ICS and noninferior to adding LABA.	N = 210, ≥18 y old. • Uncontrolled on Bec 80 µg bid • FEV$_1$ = 40%–70% • PC$_{20}$ < 12.5 mg/mL or 12% reversibility after SABA.	Randomized crossover design with three treatment periods of 14 wk each, and 2 wk of washout: • Doubling ICS (two times ICS) • Adding LABA Sal 50 µg bid • Adding Tio 18 µg qAM	Adding Tio was superior to two times ICS regarding pulmonary function (PEF, FEV$_1$) and symptom control. Adding LABA provided similar benefits to adding Tio.	Either Tio, or LABA are similar beneficial alternative therapies to add-in patients whose asthma is not well controlled on low-dose ICS.
Busse et al. (145) ICATA (Inner-City Anti-IgE Therapy for Asthma) 2011	To assess the effectiveness of omalizumab (Oma) when added to guidelines-	N = 419, 6–20 y old. • Physician-diagnosed asthma or asthma symptoms for >1 y.	Randomized to two arms: • Oma (0.016 mg/kg/1 IU/mL of serum IgE) SC	Compared to Pbo, Oma reduced days with asthma symptoms from 2 to 1.5 d/2 wk (24.5%	Add-on Oma reduced symptoms and Fall seasonal peak in asthma exacerbations.

	based therapy.	• If on SABA only: not well controlled. • If on controller: not well controlled or exacerbation in previous year.	every 2–4 wk • Pbo • Added to current asthma therapy. Duration: 60 wk.	reduction) and exacerbations.	
Zeiger et al. (146) MIST (Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers) 2011	Comparison of daily versus intermittent (prn for RTI) ICS therapy for preschoolers with recurrent wheezing and at risk for developing asthma.	N = 278, 1–4.5 y old. • Positive modified API. • ≥ 4 wheezing episodes in the previous year. • 1–6 exacerbations needing oral corticosteroid therapy in the previous year.	Randomized to three arms: • Bud neb 1 mg bid prn for RTI for 7 d • Bud neb 0.5 mg qPM • All subjects could take Alb neb qid prn. Duration: 1 y	Daily and prn Bud groups had similar rates of exacerbations as well as symptom severity, time to first exacerbation, and adverse events. Prn Bud group had 70% lower annual ICS dose.	Preschoolers with recurrent wheezing and at risk for developing asthma can be treated with ICS prn for RTI, resulting in less exposure to ICS.
Martinez et al. (147) TREXA (Beclomethasone as rescue treatment for children with mild persistent asthma) 2011	To assess the efficacy of rescue (prn) ICS versus low-dose daily ICS therapy for children with mild persistent asthma.	N = 288, 6–18 y old. • Mild persistent asthma for ≥2 y. • If on a controller medication, have well controlled	Randomized to four arms: • Bec bid plus prn Bec + Alb (Combo) • Bec bid plus prn Alb (Bec	Exacerbation rates were 31%, 28%, 35%, and 49%; and treatment failures were 5.6%, 2.8%, 8.5%, and 23%, respectively. Bec bid	Mild persistent asthma is best treated with Bec bid + Alb prn. Bec + Alb prn may be an effective step down for those well controlled on

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	asthma. • If not on a controller, have either uncontrolled asthma, or have had 1–2 exacerbations in the previous year.		• Pbo bid plus prn Bec + Alb (Bec prn) • Pbo bid plus prn Alb (Alb prn) Bec: 40 µg/dose. Duration: 44 wk	bid) provided the best outcomes, but similar to those of the Combo group. Only Combo and Bec bid caused 1.1 cm decrease in growth.	daily ICS, and it does not slow growth.
Calhoun et al. (148) BASALT (Best Adjustment Strategy for Asthma in the Long Term) 2012	To determine whether adjusting ICS dose based on FeNO, or day-to-day symptoms, is superior to guideline-informed, physician adjustment in preventing treatment failure in adults with mild-to-moderate asthma.	N = 342, ≥18 y old. • Mild-to-moderate asthma. • Controlled on low-dose ICS, Bec 80 µg bid. • FEV_1 ≥ 70% • PC_{20} < 8 mg/mL or FEV_1 ≥ 12% reversibility after SABA.	Randomized to three arms to adjust ICS dose based on: • Physician: adjusted q6wks based on asthma guidelines. • Symptoms: Bec 40 µg taken with rescue Alb prn. • FeNO: ICS dose adjusted q6wks to keep FeNO 22–35 ppb. Duration: 9 mo.	No differences in treatment failure rates: 22%, 20%, and 15%, respectively. No significant differences between guideline versus FeNO, or between guideline versus symptom.	All three modes of therapy provided similar outcomes. Neither ICS adjusted by symptoms, nor ICS adjusted by FeNO was superior to physician adjustments based on guidelines.
Kerstjens et al. (149)	To examine the efficacy of	N = 912, 1–4.5 y old.	Randomized to two arms:	Tio increased	Addition of Tio in

Study	Objective	Inclusion Criteria	Intervention	Results	Conclusion
PrimoTinA-asthma (Tiotropium for asthma poorly controlled on ICS + LABA) 2012	tiotropium (Tio) for patients with asthma poorly controlled on ICS + LABA.	• Not controlled on ICS + LABA • PostAlb $FEV_1 \leq 80\%$. • ≥1 severe exacerbation in previous 12 mo.	• Tio 5 µg qd • Pbo qd Duration: 48 wk	FEV_1 by at least 85 mL, prolonged time to first exacerbation by 25%, and reduced risk of severe exacerbations by 21% compared to Pbo.	patients uncontrolled on ICS + LABA provides modest improvement in lung function and reduced severe exacerbations.
Bacharier et al. (150) APRIL (Azithromycin for PRevention of Severe lower respiratory tract ILlnesses in Preschoolers) 2015	To evaluate whether early Azithromycin (Azi) therapy for RTI reduces progression to lung RTI requiring oral corticosteroids therapy in preschoolers with recurrent wheezing.	$N = 607$, 1–6 y old. • 1–4 wheezing episodes with RTI that required Oral corticosteroid in previous year. • Or use of controller for ≤ 8 mo in previous year.	Randomized to two arms: • Azi 12 mg/kg/d for 5 d • Pbo Alb neb prn qid. Duration: 18 mo	Azi reduced by 36% the risk of severe RTI requiring Oral corticosteroid (from 8% to 5%). Induction of Azi bacterial resistance was rare.	Among preschoolers with recurrent severe lower RTIs, the early use of Azi during RTI reduced the need for Oral corticosteroid therapy.
Wechsler et al. (151) BELT (Blacks and Exacerbations on LABA versus Tiotropium) 2015	To compare the effectiveness and safety of Tio versus LABA added to ICS in Black adults with asthma.	$N = 1,070$, 18–75 y old. • Physician-diagnosed asthma. • On ICS + LABA, or on ICS with uncontrolled asthma. • $FEV_1 \geq 40\%$.	Randomized to two arms: • Tio 18 µg qd • LABA (Sal 50 µg or For 9 µg) bid Continue ICS. Duration: 18 mo.	There were no differences between ICS + Tio versus ICS + LABA in time to first exacerbation, exacerbation rate, FEV_1, ACQ, and in patients with different B2AR genotypes.	Tio or LABA addition to ICS provides similar effectiveness in Black individuals with asthma.

Study	Objective	Population	Intervention	Results	Conclusions
Sheehan et al. (152) AVICA (Acetaminophen versus Ibuprofen in Children with Asthma) 2016	To evaluate whether acetaminophen used prn for fever or pain causes worse asthma outcomes compared to prn ibuprofen in preschoolers with mild persistent asthma.	$N = 300$, 1–5 y old. • Mild persistent asthma. • On ICS daily, prn or on Mon. • Physician-diagnosed asthma.	Randomized to two arms: • Acetaminophen 15 mg/kg prn qid for fever or pain. • Ibuprofen 9.4 mg/kg prn qid for fever or pain. Both were grape-flavored syrups. Duration: 48 wk.	There were no differences between groups on number of doses taken, exacerbation rates, rate of asthma control days, use of rescue inhaler, unscheduled health care utilization visits, and adverse events.	Among prescho with as there w differer asthma outcom betwee using acetam versus ibuprof for feve pain.
Stempel et al. (153) AUSTRI (Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone) 2016	To evaluate the risk of combined ICS + LABA and Flu + Sal versus ICS Flu alone in patients with moderate-to-severe asthma.	$N = 11,679$, ≥12 y old. • Moderate-to-severe physician-diagnosed asthma for >1 y. • Severe exacerbation in the previous year. • On daily controller.	Randomized to two arms: • Flu 100, 250, or 500 µg bid. • Sal 50 µg with Flu 100, 250, or 500 µg bid. Diskus inhaler device. Duration: 26 wk.	Rate of serious asthma-related event (death, endotracheal intubation, or hospitalization) was similar in both groups. Flu + Sal reduced by 21% the rate of severe asthma exacerbations.	Flu + S not inc risk for serious asthma event, a did red of seve asthma exacerl from 1(8%.
Stempel et al. (154) VESTRI (Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma) 2016	To evaluate the risk of combined ICS + LABA and Flu + Sal versus ICS Flu alone in children with moderate-to-severe asthma.	$N = 6,208$, 4–11 y old. • Moderate-to-severe physician diagnosed asthma for ≥1 y. • Severe	Randomized to two arms: • Flu 100 or 250 µg bid. • Sal 50 µg with Flu 100 or 250 µg bid. Diskus inhaler device.	Rate of serious asthma-related event (death, endotracheal intubation, or hospitalization) was similar in both groups. Flu + Sal reduced by	Flu + S not inc risk for serious asthma event, a did red of seve asthma exacerl

| | exacerbation in the previous year.
• On daily controller. | Duration: 26 wk. | 14% the rate of severe asthma exacerbations. | from 10 8.5%. I differe growth |

ACQ, asthma control questionnaire; AHR, airway hyperresponsiveness; AM, morning; API, asthma predictive index (155); AQLQ, asthma quality of life questionnaire; bid, twice a day; BT, bronchial thermoplasty; ED, emergency department; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting β_2 agonist; LTA, leukotriene antagonist; Neb, nebulization; OCS, oral corticosteroid; Pbo, placebo; PC_{20}, provocation concentration of methacholine that causes a 20% drop in FEV_1; PEFR, peak expiratory flow rate; q6wks, every 6 weeks; qAM, every morning; qid, four times per day; QOL, quality of life; qPM, every evening; RTI, respiratory tract illness; SABA, short-acting β_2 agonist; Sal, salmeterol; Tri, triamcinolone.

The asthma clinical trials conducted so far have defined sufficiently effective therapy for most patients with asthma. As a result, clinical research is now focusing on specific phenotypes of asthma and treatments of asthma exacerbations. Among the specific phenotypes are refractory asthma (123), asthma with accelerated loss of lung function (124), nonatopic asthma (125), patients with distinct patterns of clinical characteristics (clusters) (15,126), with distinct patterns of airway inflammation (endotypes) (127), and frequent exacerbators (128). New therapies are also needed to reverse airway remodeling and to treat acute asthma exacerbations. Exacerbations are most often precipitated by common colds and cause the most severe and costly asthma outcomes, including unscheduled visits to doctors, missed school or work days, emergency department visits, hospitalizations, intubations, and death. Current clinical trials are now investigating these remaining issues in asthma management.

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Other Immunologic Pulmonary Diseases

CHAPTER **23**

Hypersensitivity Pneumonitis*
KAREN S. HSU BLATMAN

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is a multifaceted immunologically mediated pulmonary disease with associated constitutional symptoms as a result of sensitization and then repeated inhalation of a wide variety of inhaled organic dusts. It is characterized by non–immunoglobulin E (IgE)-mediated inflammation of the pulmonary interstitium, terminal airways, and alveoli. This syndrome occurs in both atopic and nonatopic individuals and may present in several clinical forms depending on the duration, frequency, and intensity of antigen exposure; the antigenicity of the offending agent; and the patient's age and immunologic responsiveness. Most cases occur in occupational and agricultural settings. However, various hobbies and medications are also associated with HP. Despite the many antigens recognized to cause HP, the clinical, immunologic, and pathophysiologic findings are generally comparable.

ALLERGENS OF HYPERSENSITIVITY PNEUMONITIS

HP was recognized by Ramazzini (1) in 1713 in grain workers. Because awareness of this pulmonary disease has increased, there has been identification of new antigens implicated in the disease currently encompassing over 200 different agents (2). Although the immunopathophysiology of the disease is becoming clarified, there continue to be cases of HP in which the specific antigen has not been defined. The primary exposures for the development of HP are occupational, agricultural, and those related to hobbies. To reach the terminal airways and alveoli, the allergenic particles must be smaller than 3 to 5 µm. The variety of causative antigens includes airborne microbial antigens, animal or plant products, and low-molecular-weight chemicals (Table 23.1). Many of these same antigens, such as diisocyanates, mammalian and insect proteins, and wood dusts, can also induce IgE–mast cell-mediated allergic responses, including asthma.

Thermophilic actinomycetes were recognized as the causative agent in farmer's lung in 1932 in England (3). These bacteria thrive at temperatures of 70°C and can be found in high concentrations in compost piles or in silos where animal fodder is stored and becomes a culture medium for the organism. Identification and clarification of the responsible antigens has been described by a number of investigators (4,5). Increased awareness of the environmental factors favoring disease and changes in farming techniques have reduced the incidence of this disorder (6).

TABLE 23.1 SOME ANTIGENS OF HYPERSENSITIVITY PNEUMONITIS

ANTIGENS	SOURCE OF ANTIGEN	DISEASE NAME
Bacteria		
Thermophilic actinomycetes (*Saccharopolyspora rectivirgula, Thermoactinomyces vulgaris*)	Moldy hay, compost, silage, grain, moldy sugarcane	Farmer's lung, mushroom picker's lung, bagassosis
Bacillus, Klebsiella, Cytophaga	Air conditioner, humidifier	Ventilation pneumonitis, humidifier lung
Pseudomonas, Acinetobacter	Contaminated metal-working	Machine operator's lung

	fluids	
Bacillus subtilis	Enzyme dust	Enzyme/detergent worker's lung
Mycobacterium	Hot tub, metal-working fluids	Hot tub lung

Fungi

Aspergillus	Moldy brewing malt, stucco, compost, soy sauce, home contamination	Malt worker's lung, stipatosis, compost lung
Alternaria, Pullaria	Moldy redwood, wood dust	Wood worker's lung, sequoiosis
Cephalosporium	Moldy wood floors or basement, sewer water	Floor finisher's lung
Epicoccum, Rhodotorula	Cellar, bathroom and shower walls	
Penicillium	Moldy cheese, cork dust, hay, wood dust, salami seasoning, compost	Cheese worker's/washer's lung, suberosis, residential composter's lung
Penicillium, Monocillium	Moldy peat moss	Peat moss processor's lung
Cryptostroma corticale	Moldy maple bark	Maple bark disease
Trichosporum	Moldy homes in Japan	Summer pneumonitis
Pleurotus, Hypsizigus, Lyphyllum, Cortinus shiitake,	Indoor mushroom cultivation	Mushroom picker's/worker's lung

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Pholiota		
Candida	Moldy reed	Saxophonist's lung
Pezizia, Penicillium, Fusarium	Moldy home	El Niño lung
Cladosporium	Contaminated water, moldy home	Hot tub lung/sauna taker's lung
Rhizopus, Mucor	Moldy wood trimmings	Wood trimmer's disease
Amebae		
Naegleria, Acanthamoeba	Contaminated humidifier/ventilation	Ventilation pneumonitis
Animal Protein		
Avian proteins (pigeon, duck, goose, turkey, chicken, dove, parakeet, parrot, lovebird, owl, canary, pheasant)	Droppings, feather bloom	Bird/pigeon breeder's lung/disease, bird fancier's disease, budgerigar disease, plucker's lung, duck fever
Rodent urine/serum protein	Rat or gerbil urine or serum	Lab worker's lung, gerbil keeper's lung
Pearl oyster/mollusk shell protein	Shell dust	Oyster shell lung/sericulturist lung
Animal fur dust (e.g., cat)	Animal pelts, fur	Furrier's lung
Insect (grain weevil, silk worm)	*Sitophilus granarius*, silk worm larvae	Wheat weevil disease

Drugs/Medications

Amiodarone, chlorambucil, clozapine, cyclosporin, gold, β-blocker, sulfonamide, nitrofurantoin, minocycline, procarbazine, leflunomide, methotrexate	HMG-CoA reductase inhibitor, fluoxetine, roxithromycin, lenalidomide, loxoprofen, mesalamine, sirolimus, tocainamide, trofosfamide, hydroxyurea, nasal heroin, infliximab, rituximab	Drug-induced hypersensitivity pneumonitis

Chemicals

Isocyanates (TDI, HDI, MDI)	Paint/chemical catalyst, varnish, lacquer, polyurethane foam plasticizer, spandex fibers, polyurethane elastomers	Bathtub refinisher's disease, paint refinisher's disease, plastic worker's lung, chemical worker's lung
Phthalic anhydride	Heated epoxy resin, dyes, insecticides	Epoxy resin lung
Dimethyl phthalate or styrene	Chemicals used in manufacture of yachts	Yacht-maker's lung
Methylmethacrylate	Dental prosthesis making	
Others	Tobacco leaves	Tobacco grower's lung
	Insecticide	Pyrethrum lung
	Coffee bean and tea leaf dust	Coffee worker's lung, tea grower's lung
	Sawdust (pine, Cabreuva wood)	Wood worker's lung

	Fish meal extract	Fish meal worker's lung
	Veterinary feed containing soybean hulls	

HDI, hexamethylene diisocyanate; HMG-CoA, 3-hydroxy-3-methyl-glutaryl–coenzyme A; MDI, methylene diphenyl diisocyanate; TDI, toluene diisocyanate.

Both commercial and residential exposures to mold-contaminated materials have been implicated in a number of cases of HP with the descriptive names of many of these diseases reflecting the source of exposure. For example, ventilation pneumonitis, caused by contaminated heating or cooling units, is probably the most common building-related form of HP (7,8). This syndrome may occur as a result of the inhalation of aerosols-containing antigens found in small home ultrasonic humidifiers to large industrial air handling units (9). Over the past decade, respiratory illness related to inhalation of metal-working fluids (MWFs) containing Gram-negative bacteria has been reported; this finding has far-reaching consequences for industry (10–12). While fungal exposure is ubiquitous outdoors, indoor exposure in water-damaged environments is less well characterized, but many case reports incriminate fungi as the cause of the disease in both adults and children (13). The role of fungal fragments in initiating human disease has yet to be clarified, but it provides a new paradigm for fungal exposure (14). Workers cultivating mushrooms in indoor facilities have been identified as another occupation with many affected individuals (15,16). Pigeon breeders and bird fanciers have long been recognized to develop HP to inhaled antigens in dried avian droppings and feather bloom (17,18). A variety of exotic, wild, and domestic birds have also been identified as causing bird breeder's disease, including parakeets, cockatiels, doves, geese, and turkeys (19–21). Exposures to down feather pillows and comforters are also another culprit (22).

Because new cases of HP are recognized, measures to identify the antigen and decrease antigen exposure can be implemented. This recognition, as well as changes in exposure, has resulted in some hypersensitivity diseases such as smallpox handler's lung and pituitary snuff taker's lung (porcine and bovine allergens) being of historical interest only (23). Occupational exposures recently recognized include the manufacture of yacht hulls where inhalation of fumes from heated chemicals in rolling fiberglass has been implicated (24). Kiln-dried

wood heavily contaminated with Paecilomyces has affected workers in a hardwood floor processing plant (25). Inhalation of the coolant HFC134a used during laser removal of body hair has been reported to trigger HP symptoms with peripheral blood and bronchial biopsy eosinophilia (26). Cases of HP because of wind instruments contaminated with either mycobacteria or fungi have also been published (27,28).

Medications are also an important cause of pulmonary disease that resembles HP. Among the implicated medications are nitrofurantoin, amiodarone, minocycline, roxithromycin, lenalidomide, nadolol, and sulphasalazine (29–34). Intranasal heroin has also been reported to cause the syndrome (35). Because the use of biologic agents become more common, we also have seen drug-induced pneumonitis from tumor necrosis factor α (TNF-α) blockers (e.g., infliximab and etanercept) (36,37) and monoclonal antibodies, such as rituximab, an anti-CD20 IgG_1 monoclonal antibody (38).

Specific syndromes of HP occur in different parts of the world. For example, esparto grass is used in the production of rope, matting, paper pulp, and plaster in Mediterranean countries. Individuals such as stucco workers have developed HP to *Aspergillus fumigates*-contaminated esparto fiber dust in their workplace environments (39). Workers in Eastern Canada who are employed in peat moss processing plants are frequently exposed to loose dry material which may contain many microorganisms, of which molds have been implicated in causing HP (40). Summer-type HP caused by Trichosporon is an important example of a disease not found in the United States, but is the most prevalent form of HP in Japan (41). In the Midwestern United States, of 85 patients with HP identified from 1997 to 2002, the most common causes were avian-related (34%), hot tub lung (21%), farmer's lung (11%), household mold exposure (9%), and unidentified antigen (25%) (42). Controversy surrounds the classification of "hot tub lung" as HP versus infection with nontuberculous mycobacteria.

EPIDEMIOLOGY

The exact incidence of HP is unknown, but it has been identified in 2% to 8% of farmers (43) and in 6% to 21% of pigeon breeders (44). Of 36 cases of chronic HP identified by a hospital survey in Japan, reported etiologies were summer-type HP (10 cases), other home-related causes (5 cases), bird fancier's disease (7 cases), isocyanate (5 cases), farmer's lung (4 cases), and five miscellaneous cases (45). In Ireland, as haymaking methods were revolutionized in the 1980s and between 1997 and 2002, a marked decline in HP was observed (46). In the

United Kingdom, however, the overall incidence of HP is one to two cases per million workers each year. From reviewing the cases from January 1996 to December 2015, contaminated water-based MWF is the most commonly suspected culprit (35%) for occupational HP reported in the United Kingdom, compared to farming (17%) and birds (11%). Occupations reported to have been associated with HP owing to avian exposures included poultry farming and domestic bird breeding. Between 1996 and 2000, there was only one case of MWF contamination reported (47). The majority of reported cases of MWF-HP have occurred in workers manufacturing components for cars and airplanes. In the United States, the "healthy worker effect" and high employee turnover may be partly responsible for the underreporting or underrecognition of work-related cases of HP.

DIAGNOSTIC CRITERIA AND CLINICAL FEATURES

The criteria for the diagnosis of HP consist of recognizing the clinical features with supporting exposure history, laboratory, pulmonary function, and radiographic characteristics (Fig. 23.1) (48). Although there is no single confirmatory test for HP, not even lung biopsy, six significant predictors were identified that provide a 95% confidence interval. These include (a) exposure to a known offending allergen; (b) positive precipitating antibodies to the offending antigen; (c) recurrent episodes of symptoms; (d) inspiratory crackles on lung auscultation; (e) symptoms occurring 4 to 8 hours after exposure, and (f) weight loss (49). The clinical presentation follows repeated exposure and can vary from sudden and explosive systemic and respiratory symptoms to an insidious, progressive course of dyspnea, fatigue, and weight loss. Based on these clinical presentations, HP has been divided into acute, subacute, and chronic forms (50).
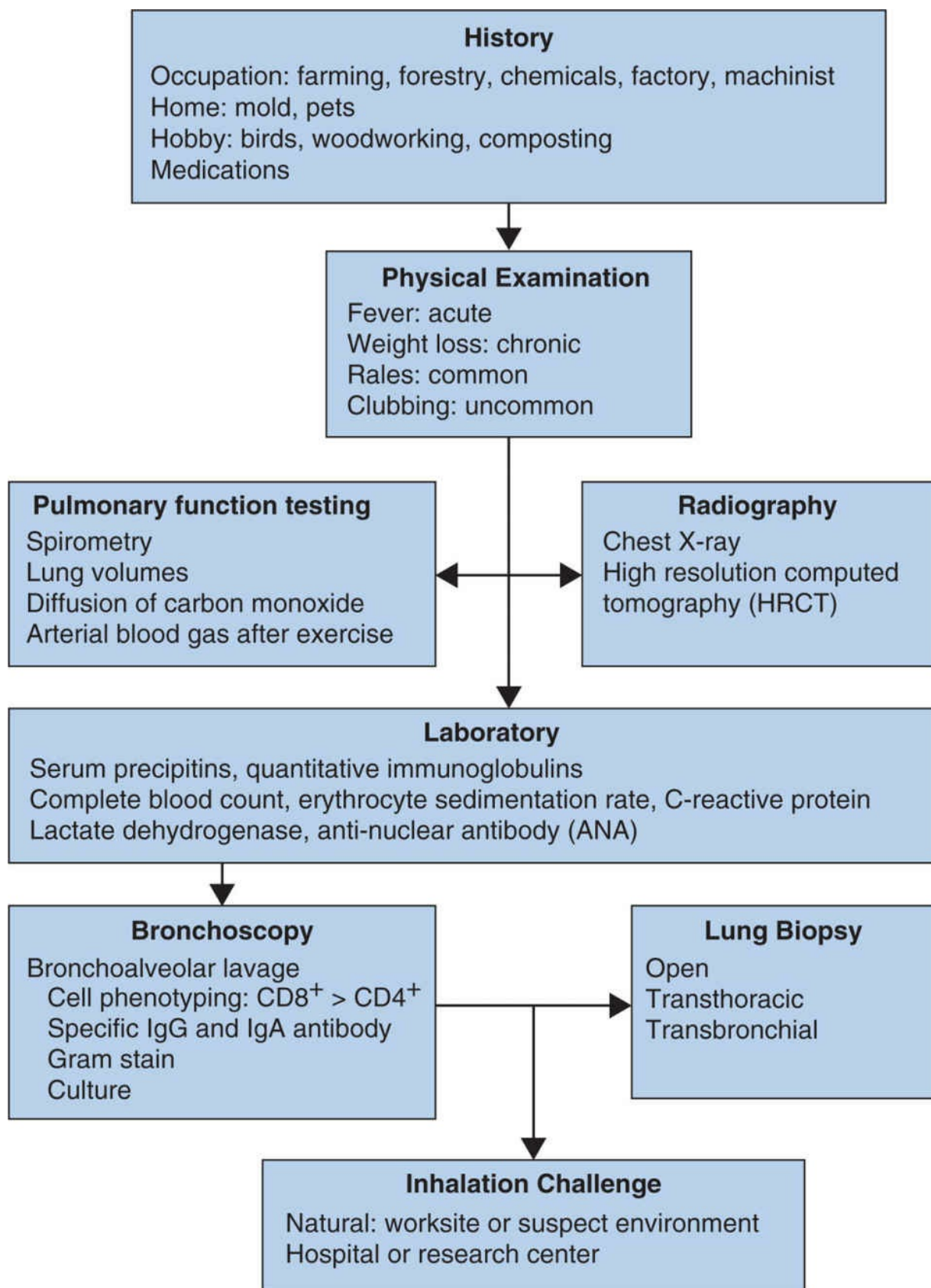
FIGURE 23.1 Evaluation of hypersensitivity pneumonitis. IgA, immunoglobin A; IgG, immunoglobin G.

The patient with the acute form presents with nonproductive cough, dyspnea,

sweating, myalgia, and malaise occurring 4 to 12 hours after intense exposure to the inciting allergen. Acute viral or bacterial infections may mimic this presentation, leading to treatment with antibiotics. With avoidance of the allergen, the symptoms spontaneously resolve over 18 to 24 hours, with complete resolution within days. This is in contrast to viral infections. On repeat exposure, the symptoms recur with either more severe and progressive symptoms or less intense and nonprogressive symptoms. The patient may recognize this pattern and try to minimize their exposure. The chronic form is characterized by the insidious onset of dyspnea that especially occurs with exertion. Other symptoms include productive cough, fatigue, and anorexia with weight loss. Fever is not typical unless there is a high-dose allergen exposure superimposed on the chronic symptoms. This form is usually related to continuous low-level antigen exposure and is not often recognized, resulting in a delay in the correct diagnosis. An antigen exposure history could be the only clue to the diagnosis. The subacute form is characterized by symptoms intermediate to the acute and chronic form with progressive lower respiratory symptoms. The acute and subacute forms may overlap clinically, just as the subacute and chronic forms may.

Lacasse et al. in 2009 published a study looking at dividing the forms into two clusters, acute and chronic HP. Lacasse et al. (51) hypothesized that the subacute form may be a variant of acute HP. In this study, nodular opacities were seen on high-resolution computed tomography (CT) in both clusters (acute versus chronic).

PHYSICAL EXAMINATION

The physical examination may be normal in the asymptomatic patient between widely spaced episodes of acute HP. Fine, dry crackles may be present, depending on the degree of lung disease present and the timing following the most recent exposure. Wheezing is not a prominent symptom. An acute flare-up of HP is associated with an ill-appearing patient in respiratory distress with temperature elevation up to 40°C for 6 to 12 hours after antigen exposure. Rash, lymphadenopathy, or rhinitis should prompt investigation for causes other than HP. With extensive fibrosis that occurs in the chronic form of the disease, dry crackles and decreased breath sounds predominate. Some patients with end-stage disease may have digital clubbing (52).

PULMONARY FUNCTION TESTS

The classic pulmonary function abnormality in the acute form is restriction with

decreased forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV$_1$) occurring 6 to 12 hours after exposure to the offending antigen (Fig. 23.2). A biphasic obstructive response similar to that seen in the early and late phases of asthma has been observed in patients who develop both occupational asthma and HP as a result of sensitization to the same antigen. Peripheral airways obstruction as determined by decreased FEV$_1$ and/or forced midrange flow measurements (FEF$_{25\%-75\%}$) has frequently been reported. Decreased gas transfer across the alveolar wall as measured by the diffusion capacity of the lungs for carbon monoxide (DL$_{CO}$) is often detected. This is in contrast to asthma, a disease in which an elevated DLCO commonly occurs. Although hypoxemia at rest may be observed with severe lung damage, hypoxemia with exercise is common and can be documented by pre- and postexercise arterial blood gas measurements. Bronchial hyperresponsiveness as determined by methacholine challenge is present in a majority of patients with HP and is likely caused by the inflammatory response of the airways. In subacute and chronic HP, there is usually a demonstrable combination of obstruction and restriction.
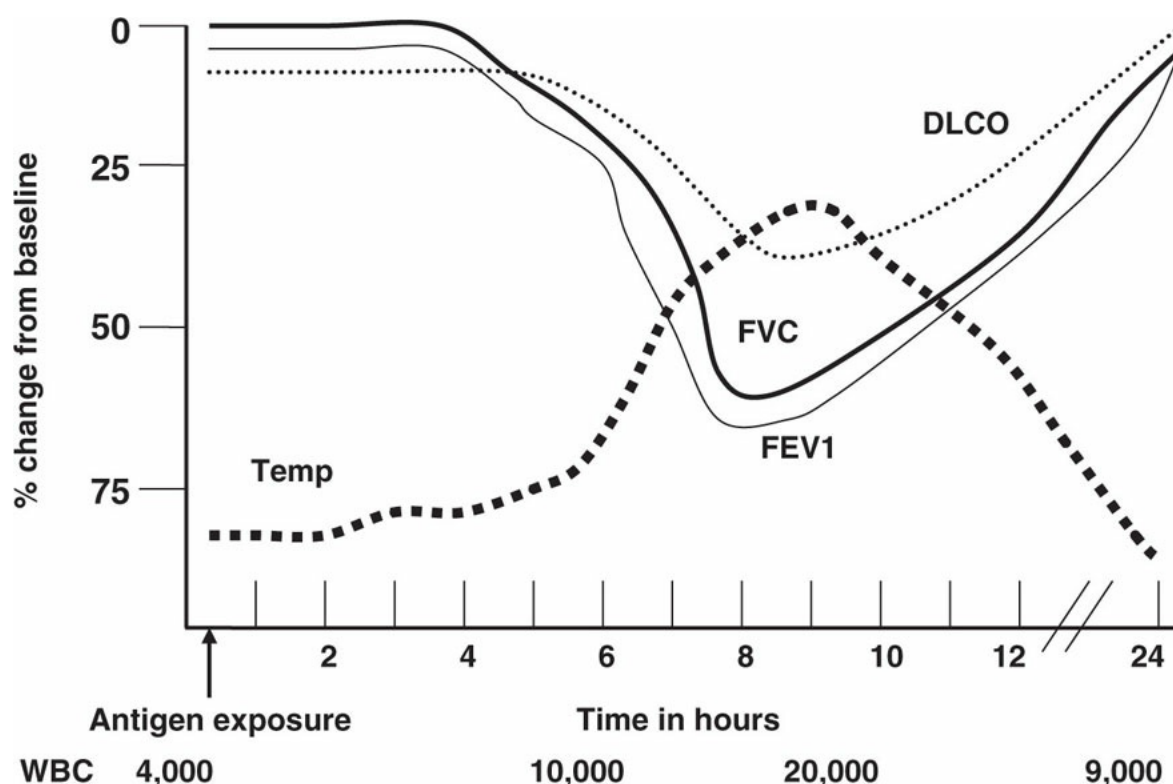
■ **FIGURE 23.2** Graphic representation of changes in acute hypersensitivity pneumonitis. DLCO, diffusion capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; WBC, white blood cell.

◾ RADIOGRAPHIC FEATURES

Chest Radiographs

Radiographic abnormalities may be transient or permanent depending on the form or stage of disease. Transient radiographic changes occur primarily in the acute form with patchy, peripheral, bilateral interstitial infiltrates with a fine, reticulonodular pattern similar to acute pulmonary edema (53) as seen in Fig. 23.3. There may be bilateral ground-glass opacities in the middle to lower lung fields that are indistinguishable from other interstitial lung disorders. Central lymphadenopathy may also be present. These changes usually resolve spontaneously with avoidance or with corticosteroid therapy. Between acute attacks, the chest radiograph is usually normal.
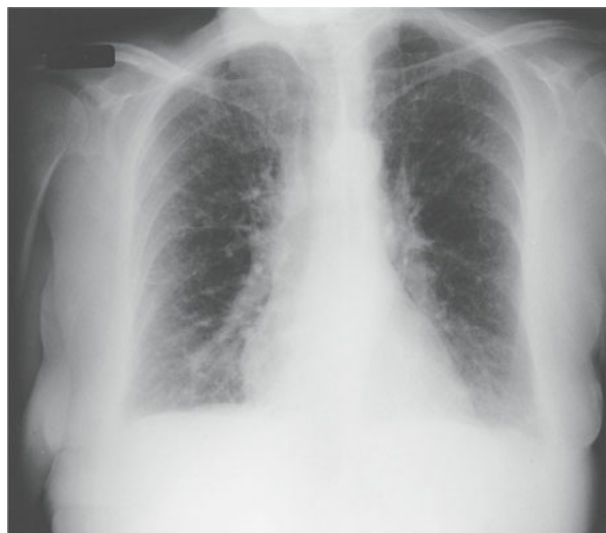
■ **Figure 23.3** Chest radiograph of a patient with hypersensitivity pneumonitis demonstrating bilateral lower-lobe patchy infiltrates and a reticulonodular pattern.

In the subacute form, nodular, patchy, or diffuse infiltrates with bilateral ground-glass opacities; poorly defined small centrilobular nodules; and lobular areas of decreased attenuation, vascularity on inspiration, and of air-trapping on expiration have been observed (54).

In the chronic form, fibrotic changes with patchy or random reticulation, traction bronchiectasis, and areas of emphysema may be seen superimposed on acute or subacute changes, typically sparing the lung bases. Less commonly, subpleural honeycombing is found (54). Findings not characteristic of HP include calcification, cavitation, atelectasis, solitary pulmonary nodules, pneumothorax, and pleural effusions.

Computed Tomography Scans

High-resolution chest CT scans may be helpful when vague parenchymal changes are present on plain chest radiographs. Findings include ground-glass opacification and diffuse consolidation suggestive of alveolar disease. A normal chest CT scan does not rule out acute HP because the sensitivity of this technique may be only 55% (55). In subacute disease, 1- to 3-mm ill-defined centrilobular nodules with superimposed areas of ground-glass opacity may be seen (56). The CT findings of the chronic form are honeycombing, pulmonary fibrosis, and traction bronchiectasis. CT features to suggest HP are predominantly middle lung involvement, extensive ground-glass opacities, and small nodules often in the central and peripheral compartments. The role of magnetic resonance imaging has been limited because of respiratory and cardiac motion artifact. Similarly, gallium lung scan and the clearance rate from the alveolar epithelium using a technetium label are being investigated in the early detection of inflammation or damage to the alveolar capillary unit, respectively, in infiltrative lung diseases, but studies specifically in HP are lacking (57).

■ LABORATORY

Routine laboratory studies are typically normal in the asymptomatic patient. In the acute form, leukocytosis with a white blood cell count to 25,000 mm^3 and a left shift, an elevated erythrocyte sedimentation rate, and decreased DLCO are common. Eosinophilia is uncommon. Total serum IgE levels are normal unless the patient has coexisting atopic disease (58). Quantitative immunoglobulin measurements are normal, or at times, serum IgG may be elevated.

The characteristic immunologic feature of HP is the presence of high titers of precipitating IgG and other classes of antibodies directed against the offending antigen demonstrated in the sera of affected patients (59). Serum precipitating antibodies, as detected by the Ouchterlony double-gel immunodiffusion technique, indicate antigen exposure, but not necessarily disease (Fig. 23.4). In pigeon breeders, as many as 50% of similarly exposed but asymptomatic individuals may have detectable precipitins (60). False-negative precipitin panels could result from omission of the responsible antigen from the test panel. Enzyme-linked immunosorbent assays and complement fixation techniques for antibody measurements may be too sensitive. However, a small study using an automated solid-phase indirect enzyme assay with fluorimetry was shown to be more sensitive in detecting symptomatic bird fanciers using antibody level of 10 mg/L in contrast to precipitin formation which detects antibody at over 40 mg/L.

The assay was rapid and may be able to differentiate between pigeon breeders who have subacute or insidious onset of chronic avian HP (61). Compared to double diffusion, electrosyneresis (electrophoresis on cellulose acetate sheets) demonstrated value to detect mold antigens in symptomatic patients, but only if the appropriate antigens were selected (62). If these tests are negative despite a suggestive history, additional testing with antigens specifically prepared from the suspect environment may be necessary. The absence of serum precipitins does not rule out HP. Routine precipitins panel may have false-negative tests, even if the correct antigen is included. Depending on the exposure, an airborne mist, fluid, dust, or soil sample from the original source may be obtained and cultured for contaminating microorganisms. This cultured material can then be used as an antigen in gel diffusion reactions.

SKIN TESTING

In contrast to asthma and other IgE–mast cell-mediated diseases, immediate wheal-and-flare skin reactivity to allergens is not useful because the immunopathogenesis of HP does not involve IgE. Skin testing with antigens that cause HP has been associated with late-onset skin reactions that histologically resemble Arthus-type reactions with mild vasculitis. On occasion, necrosis has also been observed. When differentiating IgE–mast cell-mediated occupational asthma from HP, skin testing can aid in the diagnosis. Both asthma and HP may occur in the same individual; in that case, both immediate and late reactions to antigens used in cutaneous testing may occur.

BRONCHOALVEOLAR LAVAGE

Pulmonary consultation to conduct bronchoscopy and bronchoalveolar lavage (BAL) may be indicated when other studies are normal or other diagnoses, such as tuberculosis, pulmonary sarcoidosis, alveolar proteinosis, or idiopathic pulmonary fibrosis, are entertained. Bronchoalveolar lavage fluid (BALF) is helpful in the diagnosis of HP because there is a lymphocytosis with preponderance of $CD8^+$ T lymphocytes over $CD4^+$ T cells (63). It appears to be characterized by the $CD3^+/CD8^+/CD56^+/CD57^+/CD10^-$ phenotype. The density of these phenotypic markers in BALF T lymphocytes is greater than in sarcoidosis, cryptogenic organizing pneumonia, or healthy controls (64). In addition, mast cells (greater than 1% of recovered white cells) associated with a BAL lymphocytosis may support the diagnosis of HP. The mast cells may also help in monitoring exposure because they are usually increased with acute exposure (65). An elevated lymphocyte count may not always be demonstrated

in the chronic form. In contrast to the subacute and chronic forms of HP, increased alveolar macrophages are observed in the acute form. Lymphocytosis with a normal CD4/CD8 ratio correlated with more severe interstitial disease on high-resolution CT (66). Recently, elevated levels of albumin in BALF using eriochrome cyanine R in fluorimetric determination was found in patients with HP (67). Cultures of BALF can help exclude infectious disorders.
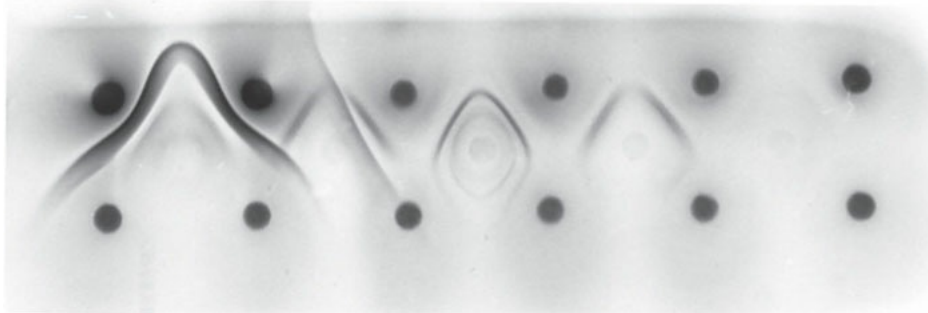
■ **Figure. 23.4** Precipitin bands detected by the Ouchterlony double-gel immunodiffusion technique.

PATHOLOGIC FEATURES

If a biopsy is deemed necessary, open lung biopsy is recommended to obtain an adequate tissue sample. Studies of transbronchial biopsy results suggest that the sample may not be adequate. Lung biopsy findings depend on the form of the disease and extent of lung damage that has occurred. The cells specifically are activated "foamy" macrophages, and have a marked predominance of lymphocytes, plasma cells, and neutrophils (68). The acute form has a marked neutrophilic infiltration in the alveoli and respiratory bronchioles with diffuse alveolar damage. Specimens of the subacute form classically reveal a triad of cellular bronchiolitis, patchy chronic interstitial lymphocytic pneumonitis, and scattered small alveolar noncaseating granulomas (54) (Fig. 23.5). The granulomas differ from pulmonary sarcoidosis in that they appear smaller, dispersed in interstitial fibrosis, loosely arranged, poorly formed, and are distributed away from bronchioles and vessels. Immunoglobulin or complement has only rarely been demonstrated in pulmonary biopsies. In the later stages of chronic HP, interstitial fibrosis with collagen-thickened bronchiolar walls and less prominent lymphocytic alveolitis is common. In chronic bird fancier's lung, nonspecific interstitial pneumonia or usual interstitial pneumonia patterns may be seen (54), compared to farmers with chronic HP develop emphysema (69).
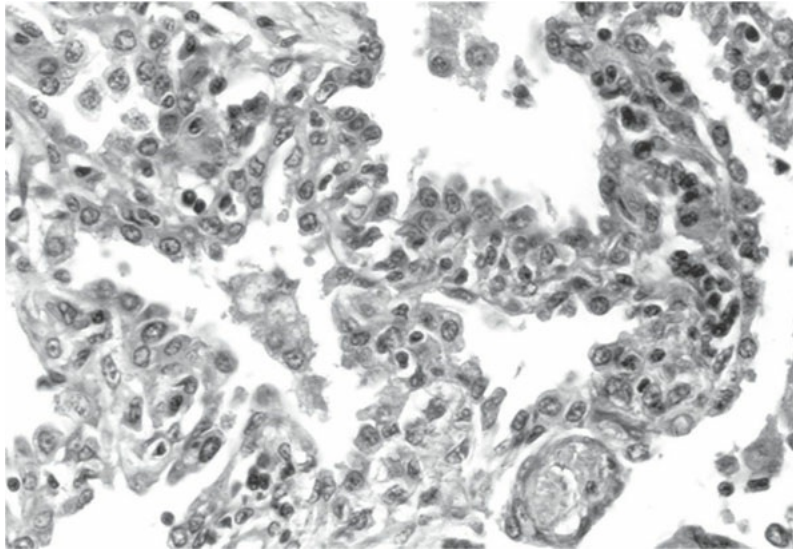
Figure 23.5 Light microscopy view of lung biopsy revealing a lymphocytic infiltrate with small noncaseating granulomas.

SPECIFIC INHALATION CHALLENGE

Although purposeful inhalation challenge is not required for diagnosis, it can be helpful in situations in which the history is convincing, but other data are lacking and the diagnosis is unclear. An allergen challenge can be performed in two ways. First, the patient can return to the workplace or the suspect environment where the antigen is present. In conjunction with pulmonary function and laboratory studies, this approach can implicate the suspect environment, but it will not necessarily identify the allergen. In evaluating these individuals, vital signs (hypoxemia), including temperature (fever), spirometry (decreased FVC), diffusing capacity, and white blood cell counts with differentials (peripheral neutrophilia), should be monitored before exposure and at intervals up to 12 hours later.

An inhalation challenge can also be performed in the hospital pulmonary function laboratory. In this situation, vital signs, including temperature, spirometry, and complete blood count, should be monitored before, during, and after a controlled antigen exposure. Unfortunately, there is generally no specified concentration of allergen or commercially available allergen preparations for this use. The concentration of antigen used can be determined by using air sampling data, which reflects usual exposure. Nonspecific antigen should also be used as a control challenge. This inhalation test requires careful observation by trained personnel because severe systemic febrile and respiratory reactions requiring intervention with corticosteroids may occur.

■ DIFFERENTIAL DIAGNOSIS

HP should be considered in any patient with acute or chronic respiratory distress with or without systemic symptoms or interstitial pneumonia (Table 23.2). Like other occupational respiratory diseases, a detailed knowledge of the work and home environment is required. Documentation of cross-shift lung function changes can be detected in some individuals. It should be noted that HP is limited to the lung, and involvement of extrapulmonary tissues has not been described.

The acute form of HP is commonly confused with atypical, community-acquired pneumonia. A group of conditions referred to as organic dust toxic syndrome (ODTS) is also often confused with HP (70). ODTS occurs in the agricultural setting, presents in individuals exposed to grain, silage, or swine materials, and primarily affects younger age groups and those without prior sensitization to offending agents. In contrast to HP, ODTS is thought to be caused by inhalation of endotoxin and other phlogistic agents. Diseases such as humidifier fever can also occur in outbreaks and may be related to inhalation of endotoxin from Gram-negative bacteria that contaminate ventilation and humidification systems (71).

TABLE 23.2 CLINICAL PRESENTATION OF HYPERSENSITIVITY PNEUMONITIS

FEATURES	ACUTE	SUBACUTE	CHRONIC
Fever, chills	+	−	−
Dyspnea	+	+	+
Cough	Nonproductive	Productive	Productive
Malaise, myalgia	+	+	+
Weight loss	−	+	+
Rales	Bibasilar	Diffuse	Diffuse

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Chest X-ray, HRCT	Nodular infiltrates	Nodular infiltrates	Fibrosis
PFTs	Restrictive	Mixed	Mixed
DLCO	Decreased	Decreased	Decreased

DLCO, diffusion capacity of the lungs for carbon monoxide; HRCT, high-resolution computed tomography; PFTs, pulmonary function tests.

Hairi et al. describe a case series of acute onset or exacerbation of HP, which includes the presence of intra-alveolar fibrin deposition in the cases, which resembled acute fibrinous and organizing pneumonia (AFOP). Given the findings by Hairi et al., (72) acute HP should be included in the differential of patients with unexplained neutrophilic capillaritis (72). Hairi et al. also supported that HP should be considered in the differential of the histologic pattern of AFOP.

The differential diagnosis of the subacute form of HP includes chronic bronchitis, recurrent episodes of influenza, and idiopathic pulmonary fibrosis. "Hot tub lung" refers to a noncaseating granulomatous lung disease with nontuberculous mycobacteria (usually *Mycobacterium avium-intracellulare*) from exposure to hot water aerosols from hot tubs or spas, showers, and indoor swimming pools (73). Immunologic pathogenesis has resulted in treatment with corticosteroids although mere abstinence from hot tubs has been successful in some cases. Whereas the chest CT scan findings are similar to HP, the histopathologic features are distinct (74,75). Like hot tub lung, nontuberculous Mycobacterium (most often *Mycobacterium immunogenum*) has been implicated with MWFs. However, detection of *M. immunogenum* in MWF is difficult. Unlike hot tub lung, mycobacteria are not cultured from BALF, and measurement of *M. immunogenum* antigens by enzyme-linked immunosorbent assay have recently been described (76).

The chronic form of HP must be differentiated from many chronic interstitial lung diseases, including idiopathic pulmonary fibrosis, chronic eosinophilic pneumonia, collagen vascular disorders (dermatomyositis), emphysema, lymphogenous spread of carcinoma, sarcoid, desquamative interstitial pneumonia, and Hamman–Rich syndrome (Table 23.3). Morell et al. (77) found

that 43% in the study initially meeting 2011 idiopathic pulmonary fibrosis criteria were finally diagnosed with HP at a later timepoint. Extrapulmonary findings of liver or spleen enlargement, generalized or local lymphadenopathy, severe sinusitis, or myositis are not consistent with HP.

PATHOGENESIS

Although the mechanisms of inflammation are complex and still not fully clarified, the Gell and Coombs type III immune complex and IV cell-mediated reactions are the best paradigm for explaining the immunologic mechanisms, resulting in HP. Several animal models and many animal studies have been conducted to elucidate the complexity of the immune inflammation-inducing disease (78–81). Unfortunately, the findings do not appear to directly parallel the inflammatory process seen in human disease. Also, there is difficulty evaluating exposed but asymptomatic animals, as can be done in human studies. Animal models suggest that HP is facilitated by the overproduction of interferon γ (IFN-γ), a helper T-cell type 1 (T_H1) response (82). This is supported by observations that interleukin 10 (IL-10), a T_H1 suppressor molecule, ameliorates the severity of the disease.

TABLE 23.3 EVALUATING CHRONIC INTERSTITIAL LUNG DISORDERS IN LUNG DISORDERS IN THE DIFFERENTIAL DIAGNOSIS OF CHRONIC HYPERSENSITIVITY PNEUMONITIS

DISEASE	ETIOLOGY	BLOOD	BAL	LUNG BIOPSY	OTHER
Pulmonary sarcoidosis	Unknown	↑ACE level, ↑IgG, ↑Calcium	CD4$^+$ alveolitis	Diffuse uniform granulomas	Hilar adenopathy, skin test anergy, gallium scan
Chronic bronchitis	Tobacco smoke	Normal	PMNs increased	Centrilobular emphysema	
Byssinosis	Cotton, flax, or hemp dust	Normal	Inflammation	NA	Reversible obstruction
Histiocytosis,	Unknown	Normal		Cytoplasmic	Pneumothorax

X/eosinophilic, granuloma				Birbeck granules	
Coal worker's pneumoconiosis	Coal dust	Normal		Focal emphysema "dust macules"	
Pulmonary alveolar proteinosis	Unknown	Normal	Saline lavage can improve function	PAS staining alveolar material, no interstitial changes	PAS material in sputum
Chronic eosinophilic pneumonia	Unknown	Eosinophilia	Eosinophilia	Eosinophils	
α_1-Antitrypsin deficiency	Genetic deficiency	Pi typing-ZZ phenotype	NA	Alveolar wall destruction	Panacinar emphysema
Sick building syndrome	Irritants	Normal	Normal	Normal	
Idiopathic pulmonary fibrosis	Unknown	Normal	Lymphocytes	Fibrosis	
Drug reactions	Drug	Eosinophils	Eosinophils, lymphs, PMNs	Variable	
Chronic granulomatous infections	Tuberculosis	Normal	Positive AFB culture	Caseating granulomas	Positive PPD
Inorganic respiratory dust syndromes	Berylliosis, silicosis	BeLPT	$CD4^+$ alveolitis, BeLPT	Granulomas, nodular silica deposits	

Chronic aspergillosis	*Aspergillus* species	Precipitating antibody, eosinophilia, elevated total and specific IgE	Few degenerating eosinophils and fungal hyphae	Exudative bronchiolitis, marked eosinophils, central saccular bronchiectasis	Positive SPT, positive sputum culture, asthma

Human studies are more difficult to perform, relying on patients who have already experienced symptoms and, therefore, not truly evaluating the course of inflammation from the onset. The relative contributions of cellular versus humoral immunity in the pathogenesis are not entirely defined. A case report of a patient with hypogammaglobulinemia and HP supports the central role of cellular immunity in mediating the disease (83).

The study data are frequently based on BAL findings compared with biopsy or peripheral blood. The data suggest that the most important elements in the inflammatory process are the activation of alveolar macrophages, $CD8^+$ cells, and T_H1 lymphocytes. The hypothesized mechanism for HP is depicted in Fig. 23.6. When antigens 2 to 10 μm in size are inhaled, they are engulfed and processed by activated alveolar macrophages that can be detected by an increase in surface IL-2R (CD25). The activated macrophages release pro-inflammatory cytokines, such as IL-1 and TNF-α (84). This in turn activates endothelial cells to increase adhesion molecules by upregulating intracellular adhesion molecule type 1 (ICAM-1) and e-selectin (85).

Antigens may also combine with antibodies, forming immune complexes that directly activate complement releasing C3a and C5a, which promote chemotaxis of neutrophils. The neutrophils release superoxide anions, hydroxyl radicals, and toxic oxygen radicals, which contribute to the inflammation.

Alveolar macrophages have cognate interaction with regulatory $CD8^+$ T lymphocytes through the T-cell receptor in the presence of B7 costimulatory molecules CD80 and CD86 on macrophages, which act as an accessory signal (86). In healthy subjects, alveolar macrophages have a normal suppressive activity. In contrast, the activated alveolar macrophages in HP increase the

antigen-presenting capacity through the increased expression of CD80 and CD86, thus enhancing the lymphocytic alveolitis. Cigarette smoking may provide a protective effect from HP by decreasing the expression of B7 costimulatory molecules, whereas viral infections could enhance HP by increasing B7 expression (87). BALF CD8$^+$ T lymphocytes release multiple T$_H$1 cell type cytokines, including IL-2, IL-8, IL-12, IL-16, and IFN-γ. These cytokines are associated with an intense inflammatory process. In direct contrast to asthma, there is an imbalance of IL-10 and IL-12. Stimulated by TNF-α, IL-10 normally functions to inhibit ICAM-1 and B7 molecule expression to prevent the alveolar macrophage from interacting with the T cell, thus preventing activation. In HP, there is a decreased production of IL-10, leading to activated macrophages and ongoing inflammation. Gene polymorphisms for TNF-α, IL-10, and TGF-β examined by restriction fragment length polymorphism analysis did not support an association between genetic control of cytokine production and disease susceptibility in 61 patients with HP compared to 101 healthy controls (88).
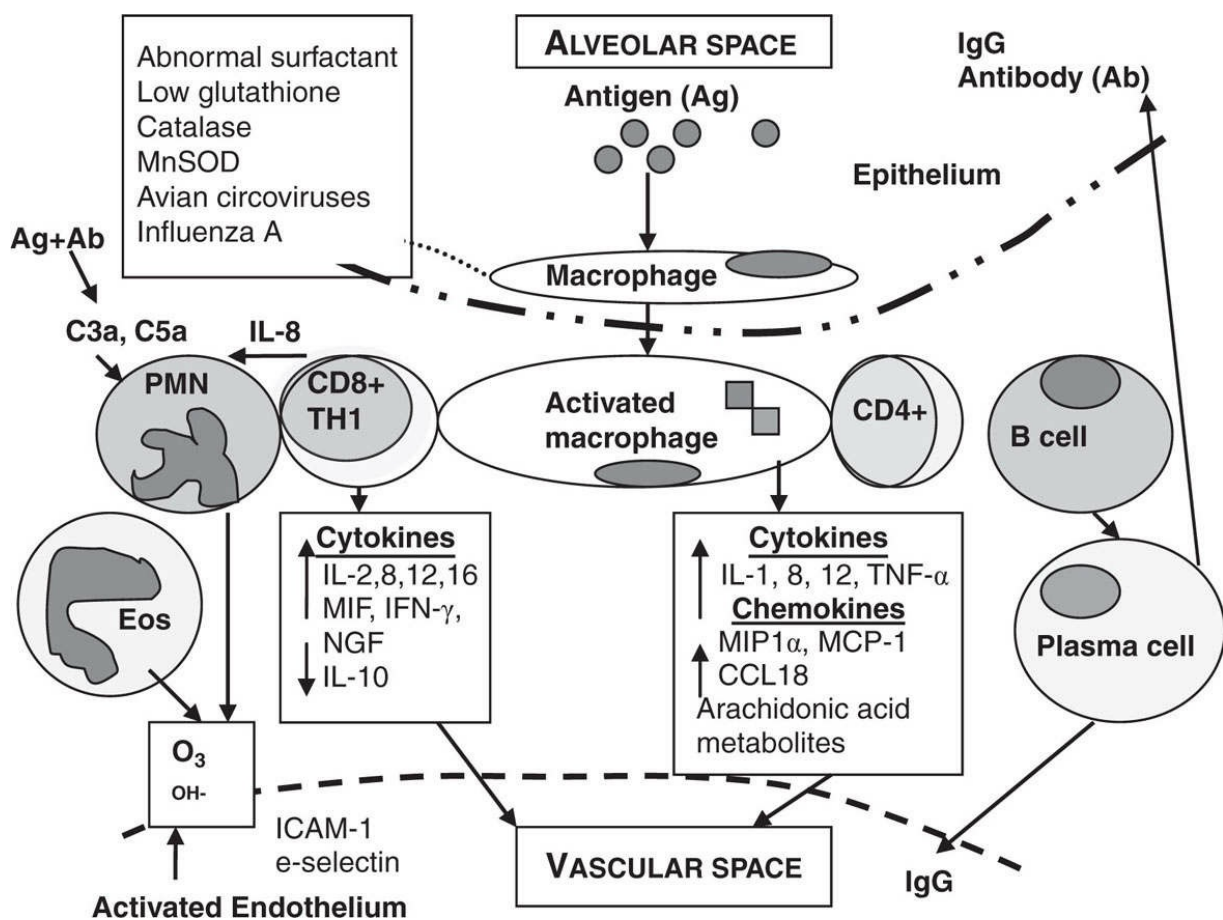
■ **Figure 23.6** Immunopathogenesis of hypersensitivity pneumonitis. IFN-γ, interferon gamma; MCP, monocyte chemoattractant protein-1; MIF, macrophage inhibitory factor; MnSOD, manganese superoxide dismutase; NGF,

nerve growth factor; PMN, polymorphonuclear leukocyte; TNF-α, tumor necrosis factor-alpha.

While HP has been classified as a Th1 disease, recent studies support that IL-17 and IL-22 secreting T_H17 cells are involved in HP. Simonian et al. (89) showed that with chronic exposure to *Saccharopolyspora retivirgula* (such as in farmer's lung), $CD4^+$ T cells were not polarized to T_H1 but rather to T_H17 with differential expression of IL-17A and IL-22. This study also supports a role for T_H17 cells in the subsequent development of lung fibrosis. Joshi et al. (90) showed that either genetic deletion or antibody-mediated depletion of IL-17 resulted in decreased inflammation and protection against HP.

BALF T cells from patients with HP have high levels of functioning IL-12R compared with peripheral blood T cells. When stimulated with recombinant IL-12, lung T cells significantly increased IFN-γ production (91). T lymphocytes along with mast cells can both produce and respond to nerve growth factor (NGF). This neurotrophic cytokine not only contributes to the development and survival of sympathetic and sensory neurons but is associated with cough and found in higher levels in asthmatics and correlates with IgE levels. In asymptomatic pigeon fanciers, serum concentrations of NGF were normal, but increased in parallel with serum CRP as a marker of inflammation. *In vitro* studies using mitogen-induced production of NGF by lymphocytes was higher than normal (92).

Natural killer T cells are a distinct subset of αβ T cells and are characterized by the co-expression of surface markers of both these cell types and release large amounts of IL-4 and IFN-γ, thus regulating the innate and adaptive immune response by modulating the T_H1/T_H2 balance. In mice, these cells can attenuate HP by suppressing the IFN-γ producing neutrophils (93).

Increased expression of the integrin $\alpha^E\beta_7$ on the surface of T cells function as mucosal homing receptors for the selective retention of T lymphocytes in lung mucosa (94). The chemokines IL-8 and monocyte chemoattractant protein-1/monocyte chemotactic and activating factor are significantly increased in BALF, suggesting a role in the accumulation of cells such as neutrophils, lymphocytes, and monocyte/macrophages into the alveoli of patients with HP (95). Arachidonic acid metabolites are released from many cell types. Along with hydrolytic enzymes, these further contribute to inflammation.

Surfactant is responsible for the regulatory activities of lung lymphocytes and alveolar macrophages. Alveolar macrophages from patients with HP enhance

phytohemagglutinin-induced peripheral blood mononuclear cell (PBMC) proliferation, whereas normal alveolar macrophages suppress this proliferation. Surfactant from normal individuals decreases mitogen-induced proliferation of PBMC greater than surfactant from patients with HP in the presence of alveolar macrophages (96). Thus, the alveolitis in HP may also be caused in part by alteration in the surfactant immunosuppressive effect.

Viruses, including influenza A, have been demonstrated by polymerase chain reaction in the lower airways of patients with acute HP. In experimental murine models infected with respiratory syncytial virus, both the early and late inflammatory responses are augmented in HP. Avian circoviruses can be detected in the T lymphocytes of respiratory organs of free-ranging and captive birds worldwide. These viruses may be potential triggers in avian-induced HP (97). Further studies are required to clarify the nature of this relationship between viral infection and the modulation of pulmonary immune response (98,99).

Recent studies have also linked Toll-like receptors (TLRs) to HP. TLRs are expressed on immune cells and recognize most antigens. In HP, when specific TLRs are activated, it is through an intracellular pathway, known as the MyD88 pathway, to release many pro-inflammatory cytokines and mediators. Nance et al. (100) have demonstrated that in mice, exposure to *S. rectivirgula,* activates MyD88, through TLR2, to initiate a cytokine and chemokine cascade, resulting in neutrophil recruitment. This has also been observed with *M. avium*-induced hypersensitivity responses, similar to the reaction found in hot tub lung (101).

MANAGEMENT

Avoidance

The most important element of management, as in any allergic lung disease, is avoidance of the offending antigen. This can occur in two ways: removal of the individual from the antigen or removal of the antigen exposure from the individual's environment. Workplace reassignment is a reasonable means of managing affected employees. Although this straightforward approach is simple to recommend, adherence by patients can be more difficult. For example, farmers afflicted with farmer's lung may be unable to change careers. Machinists with MWF–induced lung disease may be unable to work in other capacities. Pigeon breeders frequently continue intermittent pigeon exposure. Although elimination of the antigen seems essential for a long-term solution to the problem, continued antigen exposure may not lead to clinical deterioration for

some persons (102). Depending on the source of the antigen and the conditions surrounding its generation, various industrial hygiene measures have been proposed. For instance, reducing the humidity in silos has resulted in a decline in the prevalence and incidence of farmer's lung. Other measures include alterations in plant management, increased automation, improved exhaust ventilation, and personal protective face masks. Design of new facilities should reduce stagnant water prone to microbial overgrowth. Humidity of facilities should be maintained below 60%. If a facility is prone for dampness, carpeting should be avoided. Water in ventilation and air-conditioning systems should not be recirculated. Frequently, assays for the presence of the material in the environment are lacking, or the minimum concentration to provoke symptoms or initiate sensitization is not known.

Pharmacologic Treatment

Few data exist on the various pharmacologic treatments for HP. Corticosteroid therapy should be instituted in the acute and subacute forms because this has been reported to reduce symptoms and detectable inflammation and improve pulmonary function. Oral corticosteroids are recommended for acute disease starting at prednisone doses of 40 to 80 mg daily until clinical and laboratory improvements are observed, then decreased stepwise to 5 to 10 mg every other day for 6 weeks. Although indefinite corticosteroid therapy is not necessary, individualized treatment is recommended. Unfortunately, the long-term outcome of patients treated with a course of prednisone for acute farmer's lung has not always been complete recovery (103). Ongoing follow-up visits should include pulmonary function studies, not peak flow measurements, because they are not sensitive enough. Inhaled corticosteroid therapy is not as effective as oral drug therapy. If obstructive pulmonary function changes are present, then treatment with bronchodilators can be attempted. Steroid-sparing agents in the treatment of chronic progressive HP are unproven. Drugs that have shown potential *in vitro* include thalidomide because it reduces IL-18, IL-8, and TNF-α release from alveolar macrophages in interstitial lung disease. However, unfavorable side effect profiles limit current use (104). Garcia et al. (105) have demonstrated a significant increase in circulating fibrocytes in patients with HP compared to healthy individuals. However, antifibrotic agents such as nintedanib, an oral tyrosine kinase inhibitor that targets several growth factor receptors, and pirfenidone, an oral pyridine analogue that inhibits cytokines such as TNF-α and TGF-β, have not been studied in chronic HP patients.

PREVENTION AND SCREENING

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The presence of occupational lung disease in a worker usually represents a sentinel event. As in other occupational lung diseases, a systematic evaluation and investigation of the work environment and exposed cohort is recommended, although not mandated by law or always conducted (106). The investigation for additional cases may include a screening questionnaire survey with positive responses undergoing chest radiographs, serum precipitins, and lung function testing. Questionnaire surveys can be used to screen for further cases of disease, and to compare rates of symptoms between different locations in the same plant. If possible, the numbers of workers on medical leave should be reviewed. Survey questions should include demographics, risk factors, and protective factors in the home and workplace, including tobacco use and the presence of a humidifier and/or dehumidifier. Industrial hygiene surveys should include reviewing building maintenance records, visual inspection for standing water, mold growth, stained ceiling tile or carpet, roof drainage patterns, measurement of temperature and humidity, and measurement and culture of airborne, soil, or water microorganisms. In 1998, the National Institute for Occupational Safety and Health published recommended exposure limits for MWF fluids (0.4 mg/m^3 as a time-weighted average for up to 10 hours) designed to prevent respiratory disorders (107). Unfortunately, companies may not strictly enforce this exposure limit or provide specific medical surveillance programs for employees exposed to higher levels. Changes in agricultural processes, such as haymaking, can reduce the microbiologic concentrations, including fungus (108).

PROGNOSIS

There have been limited studies on the factors determining prognosis of HP. Factors identified as having predictive value in the likelihood of recovery from pigeon breeder's disease and farmer's lung include age at diagnosis, duration of antigen exposure after onset of symptoms, and total years of exposure before diagnosis. The effect of other factors, including the nature of the allergen, especially its inflammatory potential, host susceptibility, severity of lung function at diagnosis, and form of the disease, are not well clarified. Although most cases of acute disease improve, those patients with ongoing exposure continue to experience symptoms, and have abnormal lung function and abnormal chest radiographs. The mortality rates from HP range from 1% to 29% with agricultural industries closely associated with mortality. Farmer's lung deaths accounted for 40% of all HP deaths. A population-based study of 26 states using data from the National Institute for Occupational Safety and Health found Wisconsin to have the highest mortality rate at 1.04 per million and the

death rate increasing over the period 1980 to 2002 (109). It is unclear what factors account for this increase, making additional epidemiologic and surveillance research a priority in an effort to implement regional prevention and control strategies. The presence of pulmonary fibrosis is an important predictor of mortality (110). Deaths from pigeon breeder's disease have also been reported (111). The findings of fibrosis at lung biopsy or high-resolution CT indicate a poor prognosis, and the patient may die within a few years after diagnosis (112).

CONCLUSION

The diagnosis of HP requires a high index of suspicion, because the primary focus of treatment is avoidance of the offending allergen even if the specific allergen is not identified. Efforts are needed to prevent recurrent and progressive disease in individuals already sensitized and prevent potential epidemics in occupational settings. Because the diagnosis is difficult and occupational evaluation complex, a team approach, including the collaborative efforts of allergists, pulmonologists, occupational physicians, industrial hygienists, and microbiologists, is important.

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*Michael C. Zacharisen and Jordan N. Fink contributed previously to this chapter.

Allergic Bronchopulmonary Aspergillosis

PAUL A. GREENBERGER

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is characterized by immunologic reactions to antigens of *Aspergillus fumigatus* (*A. fumigatus*) that are present in the bronchial tree and result in pulmonary infiltrates, mucus plugging, and proximal bronchiectasis. ABPA initially was described in England in 1952 in patients with asthma who had recurrent episodes of fever, roentgenographic infiltrates, peripheral blood and sputum eosinophilia, and sputum production containing *A. fumigatus* hyphae (1). The first adult with ABPA in the United States was described in 1968 (2), and the first childhood case was reported in 1970 (3). Since then, the recognition of ABPA in children (4–11), adults (12–15), corticosteroid-dependent asthmatic patients (16–18), patients with cystic fibrosis (CF) (19–32), and patients with allergic fungal rhinosinusitis (33–37) and in well-controlled HIV (38) is the result of the increasing awareness by physicians and health care professionals of this complication of asthma or CF. The diagnosis has been helped by serologic tests such as total serum immunoglobulin E (IgE) (39,40), serum IgE and IgG antibodies to *A. fumigatus* (14,15,41–44), precipitating antibodies (45), and familiarity with chest radiography and high-resolution computed tomography (CT) findings, including high-attenuation mucus (46–53). In addition, when a patient presents with an unexplained radiographic opacification, thought from a neoplasm with postobstructive pneumonia, and the lesion clears with systemic steroids, this observation can lead to the diagnosis of ABPA (54). Some atypical patients seemingly have no documented history of asthma and present with chest roentgenographic infiltrates, lobar collapse, peripheral blood eosinophilia, and elevated total IgE concentration (55,56).

PREVALENCE

The prevalence of ABPA in patients with asthma is affected by the clinical

setting, geographic location, and aggressiveness of diagnostic testing. The prevalence in specialty clinics has been reported as high as 12.9% (57) and 15.8% (53) or higher. In a study published in 1991, it was estimated that the prevalence was 6.0% of 531 patients in Chicago at the Northwestern University Allergy-Immunology Service with asthma and immediate cutaneous reactivity to an *Aspergillus* mix (58). In comparison, the prevalence was 28% of such patients in Cleveland (41). These high-prevalence figures were generated from the ambulatory setting of allergist-immunologist practices where screening began with skin testing that identified *Aspergillus*-positive patients with asthma. Using data from Northwestern University that was accumulated from 2000 to 2010, the prevalence was 4.8% for patients evaluated by my five colleagues and 23.5% for patients evaluated by this author (14). The literature suggests that the overall prevalence of ABPA in patients with persistent asthma is 1% to 2.5% (58,59). ABPA has been identified on an international basis, and because of its destructive potential, it should be confirmed or excluded in all patients with persistent asthma.

CHARACTERISTICS AND RESPONSES TO *ASPERGILLUS* SPECIES,

Aspergillus species are aerobic, ubiquitous, thermotolerant, and can be recovered on a perennial basis (60–62). Spores (conidia) measure 2 to 3.5 μm and can be cultured on Sabouraud's agar slants incubated at 37°C to 40°C. Growth at this warm temperature is a somewhat unique property of *A. fumigatus*. *Aspergillus* hyphae may be identified in tissue by hematoxylin and eosin staining, but identification and morphology are better appreciated with silver methenamine or periodic acid-Schiff stains. Hyphae are 7 to 10 μm in diameter, septate, and classically branch at 45-degree angles. *Aspergillus* spores, which are often green, are inhaled from outdoor and indoor air and can reach terminal airways. They then could grow as hyphae. Airway epithelial cells phagocytose spores (63), but it is the alveolar macrophages that ingest and kill the spores (conidia) (63–65). Polymorphonuclear leukocytes (PMNs) do not ingest hyphae but bind to them and kill the hyphae by damaging their cell walls with a powerful, oxidative burst (63–66). Protection against invasive aspergillosis occurs owing to multiple factors, but most crucial is the presence of sufficient, functioning PMNs because prolonged neutropenia (<500 cells/mm^3) is a risk factor. Possibly, thrombocytopenia is also important because platelets bind to hyphae and become activated. Other predisposing factors include injured pulmonary epithelium (e.g., from chemotherapy as damaged epithelial cells are susceptible to conidia),

insufficient local complement to facilitate opsonization and the oxidative burst by PMNs, and overwhelmed innate immunity.

Aspergillus species, particularly *Aspergillus flavus* and *A. fumigatus*, produce toxic metabolites, of which aflatoxin is the most widely known. The measurement of aflatoxin is used to verify that foods, such as coffee beans and corn, are not contaminated. On a cellular level, a toxic and immunosuppressive metabolite, gliotoxin, inhibits ciliary function, macrophage phagocytosis, and lymphocyte activation (63–65). *A. fumigatus* produces proteolytic enzymes and ribosomal toxins (RNAses) (61–68) that contribute to bronchial wall damage when *A. fumigatus* hyphae are present in bronchial mucus. Epithelial cells could be damaged by proteases from *A. fumigatus* that would also decrease ciliary function. Virulence factors generated by *A. fumigatus* include elastase, phospholipase, and acid phosphatase (67,68). In that cell membranes are composed of proteins and lipids, these enzymes could destroy the cell membranes and allow for unrestrained growth of spores and resultant damage to the bronchial wall (67,68). Also, surfactant is approximately 80% phospholipid, so that the phospholipases could interfere with normal lining fluid and immune responses to *Aspergillus* species (67). Experimental evidence in mice suggests a protective role for natural killer cells and cytotoxic T lymphocytes (69).

Dendritic cells are able to phagocytize both conidia and hyphae but have opposite responses for each. After ingestion of conidia and through the Toll-like receptor 4 (TLR4), they initiate production of T_H1 cytokines tumor necrosis factor-α (TNFα), interleukin 1β (IL-1β), interferon-γ (IFNγ), and IL-12. But after ingestion of hyphae and via interaction with the TLR2 receptor, there is production of Treg and T_H2 cytokines, respectively, IL-10 and IL-4, with low levels of TNFα (70). As part of innate immunity, one of the protective, "multitasking" molecules that bind to fungi is long pentraxin 3 (71). Long pentraxin 3 facilitates opsonization of conidia by PMNs and activates TLR4/IL-1R processes and complement (71). Mice, if deficient in pentaxin 3, are very susceptible to invasive aspergillosis (71).

A. flavus and *A. fumigatus* have been incriminated in avian aspergillosis, a major economic concern in the poultry industry. For example, aspergillosis can occur in turkey poults and can cause 5% to 10% mortality rates in production flocks (72). *Aspergillus* infections are causes of abortions and mammary gland infections in sheep, as are infections in horses (pneumonia), cattle (pneumonia), camels (ulcerative tracheobronchitis), and dolphins (pneumonias including a condition resembling ABPA with cough, weight loss, and pulmonary infiltrates).

Aspergillus terreus is used in the pharmaceutic industry for synthesis of the cholesterol-lowering drug, levostatin. *Aspergillus oryzae* is invaluable in the production of soy products. *Aspergillus niger* is critical for production of citric acid. For use in the baking industry, *Aspergillus* species produce α-amylase, cellulase, and hemicellulase. Because these enzymes are powdered, some bakery workers may develop IgE-mediated rhinitis and asthma (73,74) (see Chapter 25).

The genus *Aspergillus* may produce different types of disease, depending on the immunologic status of the patient. In nonatopic patients, *Aspergillus* hyphae may grow in damaged lung and cause a fungus ball (aspergilloma). Morphologically, an aspergilloma contains thousands of tangled *Aspergillus* hyphae in pulmonary cavities, and can complicate sarcoidosis, tuberculosis, old histoplasmosis, carcinoma, CF, or ABPA (75). Hypersensitivity pneumonitis may result from inhalation of large numbers of *A. fumigatus* or *Aspergillus clavatus* spores by malt workers. These spores may also produce farmer's lung disease. *Aspergillus* species may invade tissue in the immunologically compromised (neutropenic and thrombocytopenic) host, causing sepsis and death. A rare patient, who seemingly is immunocompetent, may develop acute respiratory failure from bilateral "community-acquired" pneumonia due to *A. fumigatus* infection. *Aspergillus* species have been associated with emphysema, colonization of cysts, pulmonary suppurative reactions, and necrotizing pneumonia in other patients (76,77). In the atopic patient, fungal spore–induced asthma may occur from IgE-mediated processes in response to inhalation of *Aspergillus* spores (78,79). About 25% of patients with persistent asthma have immediate cutaneous reactivity to *A. fumigatus* or a mix of *Aspergillus* species. Why some of these patients with asthma developing ABPA remains unclear? Genetic susceptibility includes HLA-DR2+, DRB*1501, and HLA-DQ2−as well as gain of function polymorphisms for IL-4 (80–82). In immunocompetent patients, often without asthma, *Aspergillus* hyphae have been identified in eosinophilic mucoid impactions of sinuses, a condition that morphologically resembles mucoid impaction of bronchi in ABPA (37,83,84). Such allergic *Aspergillus* rhinosinusitis may occur in patients with ABPA (33,34,85) (see Chapters 10 and 12).

There are over 185 *Aspergillus* species, and additional variants and some 40 are recognized to cause disease. When *A. fumigatus* is grown in culture, changing media components and conditions alter the characteristics of the resultant strains of *A. fumigatus*. There are 25 accepted, characterized, molecular allergens of *A. fumigatus*, which are listed as *Asp f* 1-13, Asp f 15-18, 22, 23, 27-29, 34, Asp f glutathione-S-transferase, and Asp f 56 kD (see Chapter 6).

DIAGNOSTIC CRITERIA AND CLINICAL FEATURES

The criteria used for diagnosis of classic ABPA consist of five essential criteria and other criteria that may or may not be present, depending on the classification and stage of disease. The minimal essential criteria are (a) asthma, even cough-variant asthma or exercise-induced asthma; (b) central (proximal) bronchiectasis; (c) elevated total serum IgE ($\geq$417 kU/L or IU/mL or 1,000 ng/mL); (d) immediate cutaneous reactivity to *A. fumigatus*; and (e) elevated serum IgE and/or IgG antibodies to *A. fumigatus*. (15,39,42,45). Central (proximal) bronchiectasis in the absence of distal bronchiectasis, as occurs in CF or chronic obstructive pulmonary disease, is virtually pathognomonic for ABPA. Such patients are labeled ABPA-CB, for central bronchiectasis. Other features of ABPA are often present. For example, the expected diagnostic criteria (Table 24.1) of ABPA-CB include (a) asthma; (b) immediate cutaneous reactivity to *A. fumigatus*; (c) precipitating antibodies to *A. fumigatus*; (d) elevated total serum IgE concentration; (e) peripheral blood eosinophilia ($\geq$1,000/mm^3); (f) a history of either transient or fixed roentgenographic infiltrates; (g) proximal bronchiectasis; and (h) elevated serum IgE–*A. fumigatus* and IgG–*A. fumigatus* (15,39,86,87). These diagnostic criteria may not apply to ABPA-S (seropositive), where bronchiectasis cannot be detected by high-resolution chest tomography (13). Patients, who have all the criteria for ABPA but in whom proximal bronchiectasis is not present, have ABPA-S (13). The minimal essential criteria for ABPA-S include (a) asthma; (b) immediate cutaneous reactivity or *in vitro* presence of IgE to *A. fumigatus*; (c) elevated total serum IgE concentration; and (d) elevated serum IgE and IgG antibodies to *A. fumigatus* compared with sera from skin test positive patients with asthma without ABPA (13).

Other features of ABPA may include positive sputum cultures for *A. fumigatus* and a history of expectoration of golden brown plugs containing *A. fumigatus* hyphae. Patients with asthma without ABPA may have positive cutaneous tests for *A. fumigatus*, peripheral blood eosinophilia, and a history of roentgenographic infiltrates (due to atelectasis from inadequately controlled asthma). *Aspergillus* precipitins are not diagnostic of ABPA, and sputum cultures may be negative for *A. fumigatus* or even unobtainable if the patient has little bronchiectasis. In ABPA-S, bronchiectasis cannot be detected by high-resolution CT. Serologic measurements have proven useful in making the diagnosis of ABPA. A marked elevation in total serum IgE concentration and IgE and IgG antibodies to *A. fumigatus* is of value in making the diagnosis

(39,43). Furthermore, the decline in total serum IgE concentration by at least 35% by 6 weeks after institution of prednisone has been shown to occur in ABPA (40).

ABPA initially should be suspected in all patients with asthma who have immediate cutaneous reactivity to *A. fumigatus* (14). The absence of a documented chest roentgenographic infiltrate or mucoid infiltrates demonstrable by CT does not exclude ABPA-CB. Familial ABPA has been described occasionally, which emphasizes the need for screening family members for evidence of ABPA if they have asthma. Clearly, ABPA should be suspected in patients with a history of roentgenographic infiltrates, pneumonia, mucus plugging, or abnormal chest films and in patients with allergic fungal rhinosinusitis. Increasing severity of asthma without other causes may indicate evolving ABPA, but some patients present solely with asymptomatic pulmonary infiltrates. Consolidation on the chest roentgenogram caused by ABPA is often not associated with the rigors, chills, as high a fever, and overall malaise as with a bacterial pneumonia causing the same degree of roentgenographic consolidation. The time of onset of ABPA may precede recognition by many years (88–90), or there may be early diagnosis of ABPA before significant lung destruction and roentgenographic infiltrates have occurred (13). ABPA must be considered in the patient over 40 years of age with chronic bronchitis, idiopathic bronchiectasis, or interstitial fibrosis. Further lung damage may be prevented by prednisone treatment of ABPA exacerbations. The dose of prednisone necessary for controlling persistent asthma may be inadequate to prevent the emergence of ABPA, although the total serum IgE concentration may be elevated only moderately because of suppression by prednisone.

TABLE 24.1 DIAGNOSTIC CRITERIA FOR ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Asthma
Chest roentgenographic infiltrates
Immediate cutaneous reactivity to *Aspergillus*
Elevated total serum IgE concentration (>417 kU/mL)
Elevated serum IgE-Af and/or IgG-Af antibodies

Serum precipitating antibodies to Af	
Proximal bronchiectasis	
Peripheral blood eosinophilia ($\geq 1,000/mm^3$)	

MINIMAL ESSENTIAL CRITERIA FOR ABPA-CB[a]

Asthma	
Immediate cutaneous reactivity to *Aspergillus*	
Elevated total IgE concentration	
Elevated serum IgE-Af and or IgG-Af antibodies	
Proximal bronchiectasis	

[a]Suitable for diagnosis of ABPA in cystic fibrosis.

ABPA, allergic bronchopulmonary aspergillosis; Af, *Aspergillus fumigatus*; CB, central bronchiectasis; IgE, immunoglobin E.

Patients with ABPA manifest multiple allergic conditions. For example, only one of the initial 50 patients diagnosed and managed at the Northwestern University Feinberg School of Medicine had isolated cutaneous reactivity to *A. fumigatus* (91). Other atopic disorders (rhinitis, urticaria, atopic dermatitis, and drug allergy) may be present in patients with ABPA (91). The severity of asthma ranges from intermittent asthma to mildly persistent, to severe prednisone-dependent persistent asthma. Occasionally, patients deny developing wheezing or dyspnea on exposure to raked leaves, moldy hay, or damp basements, but they noted nonimmunologic triggering factors, such as cold air, infection, or weather changes. The findings in these patients emphasize that ABPA may be present in patients who appear to have no obvious IgE-mediated asthma. Such patients can present with mucoid impactions and tenacious sputum and then have the

diagnosis of ABPA made.

The number of diagnostic criteria vary depending on the classification (ABPA-CB or ABPA-S) and stage of ABPA. Furthermore, prednisone therapy causes clearing of the chest roentgenographic infiltrates, decline of the total serum IgE concentration, disappearance of precipitating antibodies, peripheral blood or sputum eosinophilia, and absence or reduction of sputum production.

PHYSICAL EXAMINATION

The physical examination in ABPA may be completely unremarkable in the asymptomatic patient, or the patient may have crackles, bronchial breathing, or wheezing, depending on the degree and quality of lung disease present. An acute exacerbation of ABPA may be associated with temperature elevation to 103°F (although this is most uncommon), with malaise, dyspnea, wheezing, and sputum production. In some cases of ABPA, extensive pulmonary consolidation on roentgenography may be accompanied by few or no clinical symptoms, in contrast to the usual manifestations of a patient with a bacterial pneumonia and the same degree of consolidation. When extensive pulmonary fibrosis has occurred from ABPA, post-tussive crackles will be present. ABPA has been associated with collapse of a lung from a mucoid impaction, and it was associated with a spontaneous pneumothorax (88). The physical examination yields evidence for these diagnoses. When ABPA infiltrates affect the periphery of the lung, pleuritis may occur, and it may be associated with restriction of chest wall movement on inspiration and a pleural friction rub. Some patients with end-stage ABPA (fibrotic stage V) have digital clubbing and cyanosis (89,90). The latter findings should suggest concomitant CF as well.

RADIOLOGY

Chest roentgenographic changes may be transient or permanent (Figs. 24.1 to 24.6) (46,47). Transient roentgenographic changes, which may clear with or without oral corticosteroid therapy, appear to be the result of parenchymal infiltrates, mucoid impactions, or secretions in damaged bronchi. These nonpermanent findings include (a) perihilar infiltrates simulating adenopathy; (b) air–fluid levels from dilated central bronchi filled with fluid and debris; (c) massive consolidation that may be unilateral or bilateral; (d) roentgenographic infiltrates; (e) "toothpaste" shadows resulting from mucoid impactions in damaged bronchi; (f) "gloved-finger" shadows from distally occluded bronchi filled with secretions; and (g) "tramline" shadows, which are two parallel hairline shadows extending out from the hilum. The width of the transradiant

zone between the lines is that of a normal bronchus at that level (46). Tramline shadows, which represent edema of the bronchial wall, may be seen in asthma without ABPA, in CF, and in left ventricular failure with elevated pulmonary venous pressure. Permanent roentgenographic findings related to proximal bronchiectasis have been shown to occur in sites of previous infiltrates, which are often, but not exclusively, in the upper lobes. This is in contrast to postinfectious bronchiectasis, which is associated with distal abnormalities and normal proximal bronchi. When permanent lung damage occurs to large bronchi, parallel line shadows and ring shadows are seen. These do not change with oral corticosteroids. Parallel line shadows are dilated tramline shadows that result from bronchiectasis; the transradiant zone between the lines is wider than that of a normal bronchus. These shadows are believed to be permanent, representing bronchial dilation. The ring shadows, 1 to 2 cm in diameter, are dilated bronchi *en face*. Pulmonary fibrosis may occur and likely is irreversible. Late findings in ABPA include cavitation, contracted upper lobes, fibrosis, and localized emphysema. When bullous changes are present, a spontaneous pneumothorax may occur (88).
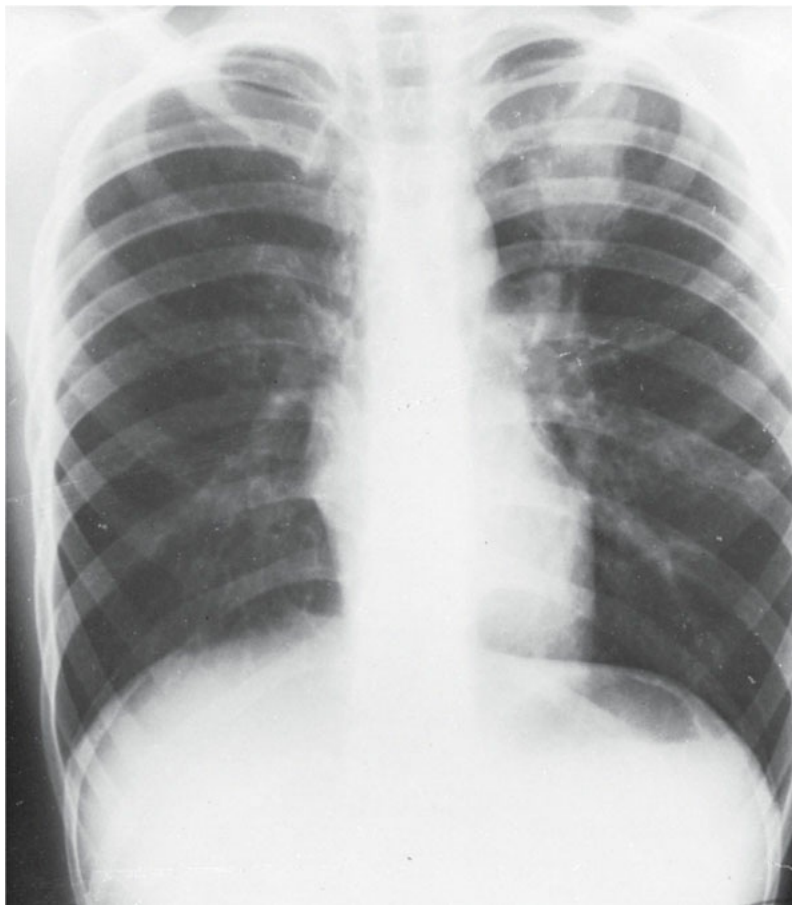
■ **FIGURE 24.1** An 11-year-old boy with far-advanced allergic bronchopulmonary aspergillosis. Presentation chest radiograph showing massive

homogeneous consolidation in left upper lobe. (Reprinted from Mintzer RA, Rogers LF, Kruglick GD, et al. The spectrum of radiologic findings in allergic bronchopulmonary aspergillosis. *Radiology*. 1978;127:301, with permission.)
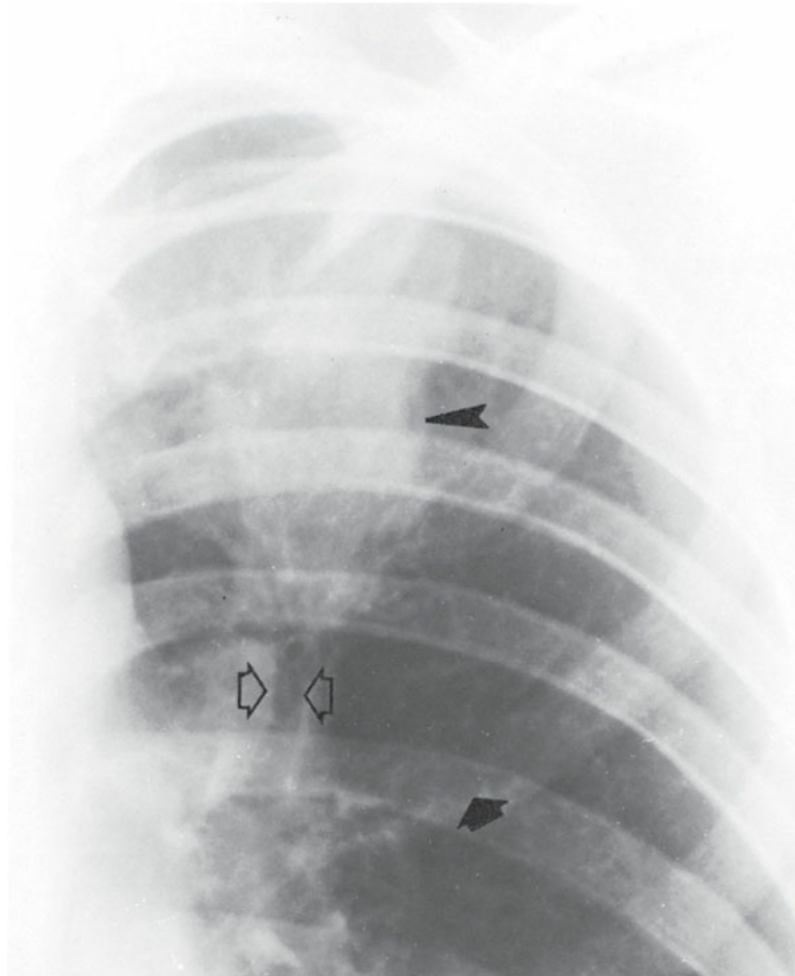
■ **FIGURE 24.2** Magnified view of the left upper lobe showing massive homogeneous consolidation (*narrow arrowhead*), parallel lines (*open broad arrowheads*), and ring shadows (*closed broad arrowhead*). (Reprinted from Mintzer RA, Rogers LF, Kruglick GD, et al. The spectrum of radiologic findings in allergic bronchopulmonary aspergillosis. *Radiology*. 1978;127:301, with permission.)

■ **FIGURE 24.3** A 31-year-old man with far-advanced allergic bronchopulmonary aspergillosis. Presentation chest radiograph. Note massive homogeneous consolidation (*large arrowhead*) and air–fluid level (*small arrowhead*). (Reprinted from Mintzer RA, Rogers LF, Kruglick GD, et al. The spectrum of radiologic findings in allergic bronchopulmonary aspergillosis. *Radiology*. 1978;127:301, with permission.)

FIGURE 24.4 Bronchogram showing classic proximal bronchiectasis with normal peripheral airways in a 25-year-old woman with allergic bronchopulmonary aspergillosis. (Reprinted from Mintzer RA, Rogers LF, Kruglick GD, et al. The spectrum of radiologic findings in allergic bronchopulmonary aspergillosis. *Radiology*. 1978;127:301, with permission.)

■ FIGURE 24.5 Post-tussive films after bronchography. Air–fluid levels (*large arrowheads*) are present in several partially filled ectatic bronchi. A bronchus in the left upper lobe is filled after the tussive effort, confirming that a portion of the density seen in this area is in fact a filled ectatic proximal bronchus (*small arrowheads*). (Reprinted from Mintzer RA, Rogers LF, Kruglick GD, et al. The spectrum of radiologic findings in allergic bronchopulmonary aspergillosis. *Radiology*. 1978;127:301, with permission.)

With high clinical suspicion of ABPA (asthma, high total serum IgE concentration, immediate cutaneous reactivity to *A. fumigatus*) and a negative chest roentgenogram, central bronchiectasis may be demonstrated by high-resolution CT (48,50,51,53). This examination should be performed as an initial radiologic test beyond the chest roentgenogram (Figs. 24.7 through 24.9). If

findings are normal, studies should be repeated in 1 to 2 years for highly suspicious cases.

■ **FIGURE 24.6** Magnified view of the left upper lung of the patient shown in Figs. 24.4 and 24.5 demonstrating parallel lines (*long arrows*) and toothpaste shadows (*arrowheads*). Perihilar infiltrates (pseudohilar adenopathy) and a gloved-finger shadow are also seen (*small arrows*). (Reprinted from Mintzer RA, Rogers LF, Kruglick GD, et al. The spectrum of radiologic findings in allergic bronchopulmonary aspergillosis. *Radiology*. 1978;127:301, with permission.)

High-resolution CT using 1.5-mm section cuts has proved valuable in detecting bronchiectasis in ABPA (48–53). The thin-section cuts were obtained every 1 to 2 cm from the apex to the diaphragm. The use of high-resolution CT examinations has identified areas of cylindrical bronchiectasis in patients with asthma. However, the areas are localized, and the patients do not have sufficient other criteria to make the diagnosis of ABPA. For example, bronchial dilatation was present in 41% of lung lobes in eight ABPA patients compared with 15% of lobes in patients with asthma without ABPA. From the axial perspective,

proximal bronchiectasis is present when it occurs in the inner two-thirds of the lung.

Bronchiectasis in ABPA may be cylindrical, cystic, or varicose (48–50). When high-resolution CT using 1 to 3 mm of collimation (thin sections) was performed in 44 patients with ABPA and compared with 38 patients with asthma without ABPA, bronchiectasis was identified in both patient groups (50). Bronchiectasis was present in 42 patients (95%) with ABPA compared with 11 patients (29%) with asthma. The CT scans revealed bronchiectasis in 70% of lobes examined in ABPA versus 9% of lobes from patients with asthma (50). Some 86% of ABPA patients had three or more bronchiectatic lobes, whereas 91% of the patients with asthma had bronchiectasis in one or two *lobes*. In the ABPA patients, bronchiectasis was varicose in 41% of patients, cystic in 34% of patients, and cylindrical in 23% of patients. Consolidation was identified in 59% of ABPA patients, primarily being located peripherally, whereas consolidation was present in 9% of patients with asthma (50). In another study, bronchiectasis, typically cylindrical, was identified in *Aspergillus*-skin test positive patients with asthma who did not have sufficient criteria for ABPA (48). These findings provide foundation for the accepted evidence of bronchial wall remodeling from airways inflammation in asthma.
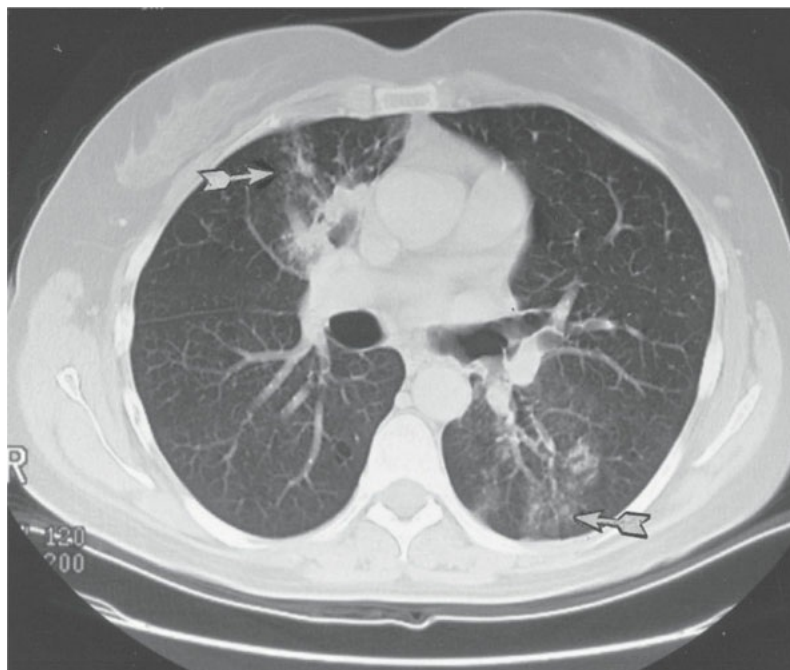
■ **FIGURE 24.7** Computed tomography scan of a 42-year-old woman demonstrating right upper lobe and left lower lobe infiltrates, the latter not seen on the posteroanterior and lateral radiographs. Dilated bronchioles are present in areas of infiltrates (*arrows*).
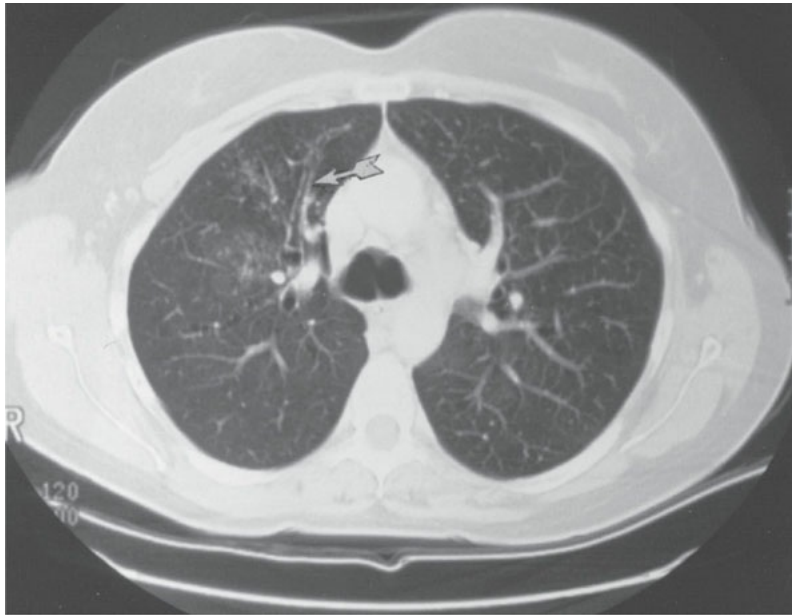
■ **FIGURE 24.8** Dilated bronchi from an axial longitudinal orientation (*arrow*) consistent with bronchiectasis (same patient as in Fig. 24.7).
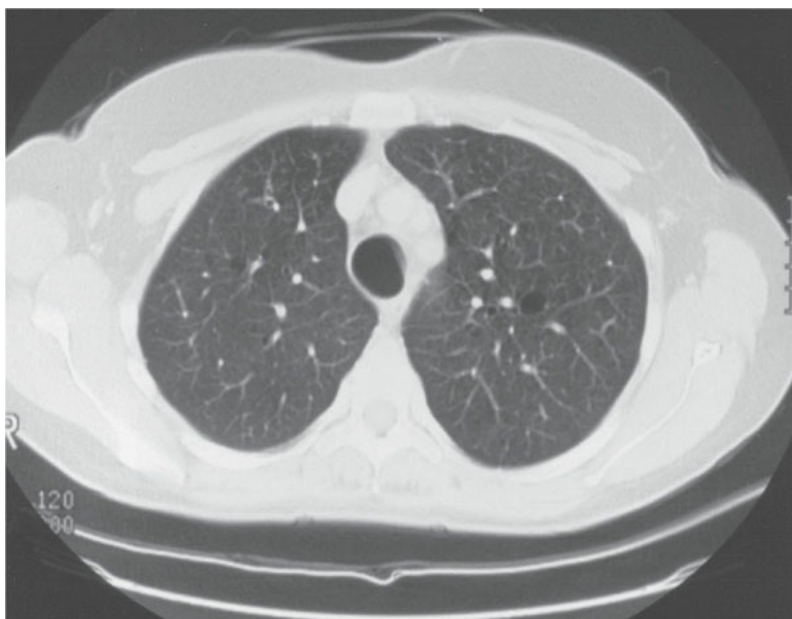
■ **FIGURE 24.9** Cystic (dilated) bronchi and bronchioles (same patient as in Fig. 24.7).

■ STAGING

Five stages of ABPA have been identified (12) namely, are acute, remission, exacerbation, corticosteroid-dependent asthma, and fibrotic. The acute stage (stage I) is present when all the major criteria of ABPA can be documented. These criteria are asthma, immediate cutaneous reactivity to *A. fumigatus*, precipitating antibody to *A. fumigatus*, elevated serum IgE concentration, which is over the upper limit of normal adults (>417 kU/L), peripheral blood

eosinophilia, history of or presence of roentgenographic infiltrates, and proximal bronchiectasis, unless the patient has ABPA-S. If measured, sera from stage I patients have elevated serum IgE and IgG antibodies to *A. fumigatus* compared with sera from patients with asthma and immediate cutaneous reactivity to *A. fumigatus* but not sufficient criteria for ABPA. After therapy with prednisone, the chest roentgenogram clears and the total serum IgE concentration declines substantially (12,15,39,40). Remission (stage II) is defined as clearing of the roentgenographic lesions and decline in total serum IgE for at least 6 months. Exacerbation (stage III) of ABPA is present when, after the remission that follows prednisone therapy, the patient develops a new roentgenographic infiltrate, total IgE concentration rises over baseline, and the other criteria of stage I appear. Corticosteroid-dependent asthma (stage IV) includes patients whose prednisone cannot be terminated without occurrence of persistent moderate-to-severe allergic asthma requiring oral corticosteroids for control or new roentgenographic infiltrates. Despite prednisone administration, most patients have elevated total serum IgE concentrations, precipitating antibody, and elevated serum IgE and IgG antibodies to *A. fumigatus*. Roentgenographic infiltrates may or may not occur. Stage V ABPA is present when extensive cystic or fibrotic changes are demonstrated on the chest roentgenogram (89,90). Patients in the fibrotic stage have some degree of irreversible obstructive flow rates on pulmonary function testing. A reversible obstructive component requires prednisone therapy, but high-dose prednisone does not reverse the roentgenographic lesions of irreversible obstructive disease. At the time of the initial diagnosis, the stage of ABPA may not be defined, but it becomes clear after several months of observation and treatment.

Patients with ABPA-S can be in stages I through IV, but not stage V (13). Patients with ABPA and CF are often in stage III (recurrent exacerbation) but may be in any stage.

LABORATORY AND TEST FINDINGS

All patients exhibit immediate cutaneous reactivity (wheal and flare) to *A. fumigatus* antigen. Because of the lack of standardized *A. fumigatus* antigens for clinical testing, differences in skin reactivity have been reported by different researchers (Table 24.2) (86,92–94). Approximately 25% of patients with asthma without ABPA demonstrate immediate skin reactivity to *A. fumigatus*, and about 10% show precipitating antibodies against *A. fumigatus*. Conversely, a nonreactive skin test (prick and intradermal) to reactive extracts of *A. fumigatus* essentially excludes the diagnosis of ABPA (14). Some commercial mixes of

Aspergillus species contain little or no *A. fumigatus*; it is advised to skin test with a reactive extract of *A. fumigatus*.

Some ABPA patients display a biphasic skin response to the intradermal injection of *A. fumigatus* antigen. This consists of a typical immediate wheal and flare (erythema) seen within 20 minutes, which subsides, to be followed in 4 to 8 hours by erythema and induration that resolves in 24 hours. Initially, IgG, IgM, IgA, and C3 had been identified on biopsies of these late, cutaneous reactions, consistent with features of an Arthus (type III) immune response (95). IgE antibodies subsequently were found to participate in the late reactions with little evidence of immunoglobulin, complement, or immune complexes (96). Furthermore, some of the edema and induration can be attributable to the potent vasodilator, calcitonin gene-related peptide, and permeability factor, vascular endothelial growth factor that have been found during late-phase cutaneous reactions (to pollen, cat, and dust mite allergens) (97). Few ABPA patients treated at the Northwestern University Feinberg School of Medicine have biphasic skin reactivity despite the presence of anti-*A. fumigatus* IgE antibodies and precipitating antibodies. Conversely, few patients are tested by intradermal injection, because skin-prick test results are positive in nearly all patients. As shown in Table 24.2, precipitating antibody to *A. fumigatus* is not uncommon in patients without ABPA and likely represents previous exposure to *A. fumigatus* antigens. In ABPA, however, these antibodies may be important in the pathogenesis of the disease, or at least a manifestation of very high levels of anti-*A. fumigatus* IgG antibody production.

TABLE 24.2 INCIDENCE OF IMMUNOLOGIC REACTIONS TO *ASPERGILLUS FUMIGATUS*

PATIENTS STUDIED	IMMEDIATE SKIN REACTIVITY (%)	PRECIPITINS (%)
Normal population	1–4	0–3
Hospitalized patients		2.5–6
Asthma without aspergillosis	12–38	9–25
Asthma without aspergillosis[a]		

London	23	10.5
Cleveland	28	7.5
ABPA	100	100[b]
Aspergilloma	25	100
Cystic fibrosis	39	31

[a]Similar antigenic material used for both groups.

[b]May be negative at times.

Data from Hoehne JH, Reed CE, Dickie HA. Allergic bronchopulmonary aspergillosis is not rare. *Chest*. 1973;63:177; Longbottom JL, Pepys J. Pulmonary aspergillosis: diagnostic and immunologic significance of antigens and C-substance in *Aspergillus fumigatus*. *J Pathol Bacteriol*. 1964;88:141; Reed C. Variability of antigenicity of *Aspergillus fumigatus*. *J Allergy Clin Immunol*. 1978;61:227; Rosenberg M, Patterson R, Mintzer R, et al. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. *Ann Intern Med*. 1977;86:405; and Schwartz HJ, Citron KM, Chester EH, et al. A comparison of the prevalence of sensitization to *Aspergillus* antigens among asthmatics in Cleveland and London. *J Allergy Clin Immunol*, 1978;62:9.

A. fumigatus extracts are mixtures containing well over 400 distinctive proteins and additional glycoproteins, polysaccharides, and other metabolites with biologic functions (98–100). This has led to attempts at utilization of recombinant allergens for diagnosis (98,99,101–104). There is marked heterogeneity of immunoglobulin and lymphocyte binding on stimulation with *A. fumigatus* allergens (98). From the historic perspective regarding methodology, after rocket immunoelectrophoresis of *A. fumigatus* mycelia and addition of *A. fumigatus* antisera raised in rabbits, 35 different bands could be detected. Immunoblotting then resulted in identification of 100 proteins (glycoproteins) that bind to immunoglobulins (98). As of now, it can be stated that the even larger number of proteins, glycoproteins, polysaccharides, and metabolic products with biologic function is a testament to the challenges of identifying critical *immunodominant* peptides and allergens that would be useful in diagnosis (105).

One characterized polypeptide is *Asp f* 1 and has a molecular weight of 18,000 Da. It is generated from a culture filtrate that was found to react with IgE and IgG antibodies and was toxic to lymphocytes (63). *Asp f* 1 is a member of the mitogillin family, which demonstrates ribonuclease (ribotoxic) activity. Sera from ABPA patients react with several ribotoxins, and far greater quantities of IgE and IgG antibodies to ribotoxins from *Aspergillus* are present in patients with ABPA as compared with nonatopic patients with asthma (63). In diagnosis, utilizing assays for both anti-IgE antibodies to *Asp f 1* and *Asp f 2* shows some discrimination from asthma (106). Some peptides (12 to 16 amino acids from *Asp f* 1) induce T_H1, and others produce T_H2 cytokine responses. Peptides that are three to seven amino acids long have been obtained from the IgE-binding region of *Asp f* 2 and evaluated for IgE binding with sera from ABPA patients. Overall, just a few amino acids of *Asp f* 2 provide the conformation to react with IgE, whereas these short IgE-specific peptides did not react with IgG antibodies (103,105). These results emphasize the just a few of the complexities to be addressed in the future in terms of developing diagnostic tests. Reactive epitopes of *A. fumigatus* are under investigation for use in skin testing and *in vitro* assays. It is hoped that more precise skin testing and *in vitro* test results using recombinant, molecularly based allergens will lead to more accurate diagnoses. However, such an approach, at least with even with ragweed proteins for allergic rhinitis, was unsuccessful in that a particular "immunologic fingerprint" did not occur as hypothesized. The genotypes were different for the "hay fever" phenotype.

In the double-gel diffusion technique, most patients' sera have at least one to three precipitin bands to *A. fumigatus*. Some sera must be concentrated five times to demonstrate precipitating antibody. A precipitin band with no immunologic significance may be seen, caused by the presence of C-reactive protein in human sera that cross-reacts with a polysaccharide antigen in *A. fumigatus*. This false-positive band can be avoided by adding citric acid to the agar gel. It is not essential to require the presence of precipitating antibodies for the diagnosis of ABPA (14).

Because of the high incidence of cutaneous reactivity and precipitating antibodies to *A. fumigatus* in patients with CF and transient roentgenographic infiltrates attributed to *A. fumigatus,* there is concern that *A. fumigatus* bronchial colonization or ABPA itself could contribute to the ongoing lung damage of CF. Nevertheless, this notion has produced conflicting results (107,108). The use of high-dose tobramycin by nebulization might favor the growth of *A. fumigatus* in the bronchial mucus of CF patients. The question has also been raised whether

ABPA might be a variant form of CF. Genetic testing has identified the ΔF508 mutation in one allele of some ABPA patients or other variant patterns (30,109). Eleven patients with ABPA who had normal sweat electrolytes (≤40 mM) had extensive genetic analysis of the coding region for the CF transmembrane regulator. Five patients had one CF mutation (ΔF508 in four and R117H in one), whereas another patient had two CF mutations (ΔF508/R347H). In comparison were 53 patients with chronic bronchitis, none of whom had the ΔF508 mutation, demonstrating clear-cut differences and suggesting that ABPA in some patients includes CF heterozygosity. In a study of 16 patients with ABPA, six patients (37.5%) were homozygous for ΔF508 and six were heterozygous with other mutations in four patients (28). In our patient population, all but one patient tested had normal sweat chloride concentrations in the absence of CF. Nevertheless, there is consistent evidence that ABPA can complicate CF, and it must be considered in that population because about 8.9% (range 3% to 25%) of patients with CF have ABPA (110). The prevalence of sensitization to *A. fumigatus*, by skin testing or *in vitro* measurement in CF, is even higher with a pooled prevalence of 39.1% (range 20% to 65%) (110).

Serum IgE concentrations in patients with ABPA are elevated, but the degree of elevation varies markedly. In most patients, the total serum IgE concentration is greater than 417 kU/L (417 IU/mL or 1,000 ng/mL) (1 kU/L = 1 IU/mL = 2.4 ng/mL). It has been demonstrated that *A. fumigatus* growing in the respiratory tract without tissue invasion, as in ABPA, can provide a potent stimulus for production of total "nonspecific" serum IgE (111). When serum IgE or serum IgG antibodies, or both, against *A. fumigatus* are elevated compared with sera from skin-prick–positive asthmatic patients without evidence for ABPA, ABPA is highly probable or definitely present (14,15,42,43). With prednisone therapy and clinical improvement, the total IgE concentration and IgE–*A. fumigatus* decrease, although at different rates. Seemingly, this decrease is associated with a decrease in the number of *A. fumigatus* organisms in the bronchi and suppression of CD4T_H2 allergic inflammation. It is possible, but unlikely, that the reduction in IgE concentration is directly because of prednisone without an effect on *A. fumigatus* in the lung, because in other conditions, such as atopic dermatitis and asthma, corticosteroids did not lower total serum IgE concentrations significantly (112,113).

Because of the wide variation of total serum IgE concentrations in atopic patients with asthma, some difficulty exists in differentiating the patient with ABPA from the patient with asthma and cutaneous reactivity to *A. fumigatus*, with or without precipitating antibody to *A. fumigatus* and a history of an

abnormal chest roentgenogram. Detection of elevated serum IgE and IgG antibodies to *A. fumigatus* has proved useful to identify patients with ABPA (14,15,42,43). Sera from patients with ABPA have at least twice the level of antibody to *A. fumigatus* than do sera from patients with asthma with skin-prick–positive reactions to *A. fumigatus*. During other stages of ABPA, the indices have diagnostic value if results are elevated, but are not consistently positive in all patients. In patients with suspected ABPA, sera should be obtained and serodiagnosis should be attempted before prednisone therapy is started so that the total IgE concentration is at its peak. Hyperimmunoglobulinemia E should raise the possibility of ABPA in any patient with asthma, although other causes besides ABPA include atopic dermatitis, hyper-IgE syndrome, chronic granulomatous disease (if ABPA is present), other immune deficiency, eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome), allergic bronchopulmonary mycosis (ABPM), parasitism, and, remotely, IgE myeloma.

Lymphocyte transformation to *A. fumigatus* is present in some cases but is not a diagnostic feature of ABPA or consistently elevated during exacerbations (86). Delayed hypersensitivity (type IV) reactions occurring 48 hours after administration of intradermal *A. fumigatus* antigens typically are not seen (114).

T- and B-cell analysis of selected patients with ABPA has not shown abnormal numbers of B cells, CD4 (helper), or CD8 (suppressor) cells. However, some patients have evidence for B-cell activation (CD19$^+$ CD23$^+$) or T-cell activation (CD3$^+$ CD25$^+$). T-cell clones from peripheral blood from three ABPA patients, two of whom had been in remission, were generated and analyzed (115). The clones were specific for *Asp f* 1 and were reported to be HLA class II molecules restricted to HLA-DR2 or HLA-DR5 alleles. Furthermore, the T-cell clones produced high quantities of IL-4 and little IFNγ, consistent with helper T-cell type 2 (T$_H$2 subtype of CD4$^+$ cells). Additional experiments explored major histocompatibility complex (MHC) class II restriction in 15 additional ABPA patients to determine whether specific HLA class II molecules were likely associated with *A. fumigatus* presentation (116). Of 18 patients (88.8%) overall, 16 were either HLA-DR2 or HLA-DR5 compared with 42.1% frequency in normal individuals (116). Using polymerase chain reaction techniques to investigate HLA-DR subtypes, it was determined that three HLA-DR2 alleles (identified as subtypes DRB1 1501, 1503, and 1601) and three HLA-DR5 alleles (identified as subtypes DRB1 1101, 1104, and 1202) were recognized by T cells in their activation (116). In other words, T-cell activation after binding to *Asp f* 1

was restricted to certain subtypes of class II molecules HLA-DR2 or HLA-DR5, raising the possibility that selective HLA-DR alleles might provide the genetic disadvantage that permits T-cell activation and, possibly, ABPA to evolve. Because not all patients with these genotypes have ABPA, additional insight is attributable to gain of function polymorphisms for IL-4 in ABPA (81). Using CD20 (B cells), incubation with IL-4 increases the number of CD23 (FcεRII) molecules on the CD20 cells, being greater in ABPA than non-ABPA cell populations (81). This process could facilitate antigen presentation by B cells. Genetic susceptibilities affecting surfactant proteins and TLR9 have been described (18).

Circulating immune complexes with activation of the classic pathway during an acute flare-up of ABPA has been described (117). Although Clq precipitins were present in patient sera, it was not proven that *A. fumigatus* antigen was present in these complexes. ABPA is not considered to be characterized by circulating immune complexes as in serum sickness. But it has been demonstrated that *A. fumigatus* can convert C3 proactivator to C3 activator, a component of the alternate pathway (118). It is known that secretory IgA can activate the alternate pathway, and that *A. fumigatus* in the bronchial tract can stimulate IgA production (119).

In vitro basophil histamine release resulted from exposure to an *Aspergillus* mix, anti-IgE, and other fungi in patients with ABPA and fungi-sensitive asthma (with immediate cutaneous reactivity to *A. fumigatus*) (120). There was much greater histamine release to *Aspergillus* and anti-IgE from basophils of patients with ABPA than there was from fungi-sensitive asthmatic patients without ABPA. Furthermore, patients with stage IV and stage V ABPA demonstrated greater histamine release to *A. fumigatus* than did patients in stage I, II, or III. There was greater histamine release to other fungi from cells taken from ABPA patients than there was from other patients with asthma. These data document a cellular difference in ABPA patients when compared with fungi-sensitive asthmatic patients. There was no difference between ABPA patients and patients with asthma in terms of cutaneous endpoint titration using a commercially available *Aspergillus* mix (120). With flow cytometry, basophil reactivity to *A. fumigatus* has been reported in patients with CF who have ABPA or are sensitized to *A. fumigatus* without having ABPA (121,122). When basophils are positive for the surface activation marker CD203c after incubation with *A. fumigatus*, they are considered upregulated. The basophil marker, CD63, which has kinetics similar to histamine, can also be stimulated by *A. fumigatus* but did not add to discrimination in addition to testing for CD203c (122). The stimulated

basophils from patients with CF and ABPA show much higher activation (CD203c levels) than stimulated basophils from patients who are sensitized to *A. fumigatus* but do not have ABPA (121). There was a negative correlation between CD203c levels of stimulated basophils and FEV_1 in *A. fumigatus* sensitized patients (but not in nonsensitized patients) (121). Basophils are surrogates for mast cells, which primarily reside in tissue. The basophil stimulation test may provide an extension of what it means to be sensitized beyond positive immediate skin test and *in vitro* detection of anti-allergen IgE.

A positive sputum culture for *A. fumigatus* is a helpful, but not pathognomonic, feature of ABPA. Repeated positive cultures may be significant. Whereas some patients produce golden brown plugs or "pearls" of mucus containing *Aspergillus* mycelia, others produce no sputum at all, even in the presence of roentgenographic infiltrates. Sputum eosinophilia is usually found in patients with significant sputum production, but is not essential for diagnosis and clearly is not specific.

Peripheral blood eosinophilia is common in untreated patients, but need not be extremely high, and is often about 10% to 25% of the differential in patients who have not received oral corticosteroids. Bronchial inhalational challenges with *A. fumigatus* are not required to confirm the diagnosis and are not without risk. Nevertheless, a dual reaction usually occurs after bronchoprovocation. An immediate reduction in flow that resolves, to be followed in some cases by a recurrence of obstruction after 4 to 10 hours, has been described (95). Pretreatment with β-adrenergic agonists prevents the immediate reaction; pretreatment with one dose of inhaled corticosteroids reduces the extent of the late reaction; and cromolyn sodium has been reported to prevent both. Inhalational challenge with *A. fumigatus* in a most skin test positive patients with asthma produces the immediate response only. Aspergilloma patients may respond only with a late pattern.

LUNG BIOPSY

Because of the increasing recognition of ABPA, the need for lung biopsy in confirming the diagnosis appears unnecessary unless other diseases must be excluded. Bronchiectasis in the affected lobes in segmental and subsegmental bronchi, with sparing of distal branches, characterizes the pattern of proximal or central bronchiectasis (123–125). Bronchi are tortuous and very dilated. Histologically, bronchi contain tenacious mucus, fibrin, Curschmann spirals, Charcot–Leyden crystals (eosinophil-derived lysophospholipase), and

inflammatory cells (mononuclear cells and eosinophils) (123–126). Fungal hyphae can be identified in the bronchial lumen, and *A. fumigatus* can be isolated in culture. Except for a few unusual case reports, no evidence exists for invasion of the bronchial wall, despite numerous hyphae in the lumen. Bronchial wall damage is associated with the presence of mononuclear cells and eosinophils, and in some cases with granulomata. Organisms of *Aspergillus* may be surrounded by necrosis, or acute or chronic inflammation. In other areas, there is replacement of submucosa with fibrous tissue. It is not known why bronchial wall destruction is focal with uninvolved adjacent areas.

A variety of morphologic lesions have been described in patients meeting criteria of ABPA (123–125). These include *A. fumigatus* hyphae in granulomatous bronchiolitis, exudative bronchiolitis, *A. fumigatus* hyphae in microabscess, eosinophilic pneumonia, lipid pneumonia, lymphocytic interstitial pneumonia, desquamative interstitial pneumonia, pulmonary vasculitis, and pulmonary fibrosis. Some patients with ABPA may show pathology consistent with bronchocentric granulomatosis. Mucoid impaction related to ABPA may cause proximal bronchial obstruction with distal areas of bronchiolitis obliterans. Examples of a cavitary mass (Figs. 24.10 and 24.11) and microscopic sections are shown in Figs. 24.12 and 24.13.
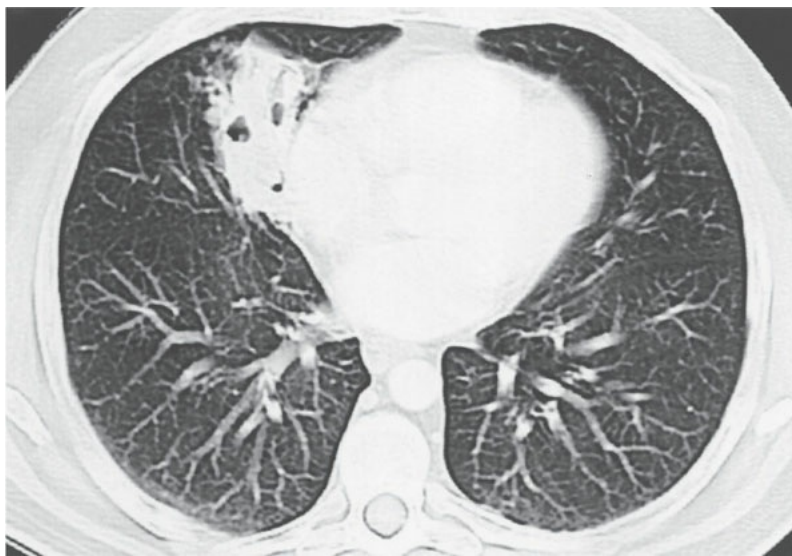
■ **FIGURE 24.10** Computed tomography scan demonstrating a cavitary mass in the right lower lobe in a 56-year-old man. The total serum IgE was 4,440 ng/mL. His only symptom was a mild nonproductive cough.
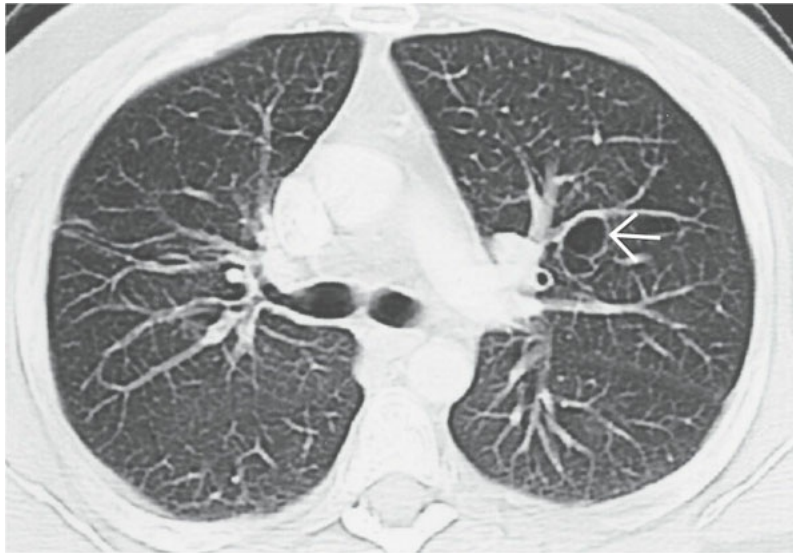
FIGURE 24.11 The same patient as in Fig. 24.10. The computed tomography scan at the level of the carina demonstrating cystic bronchiectasis (*arrow*).
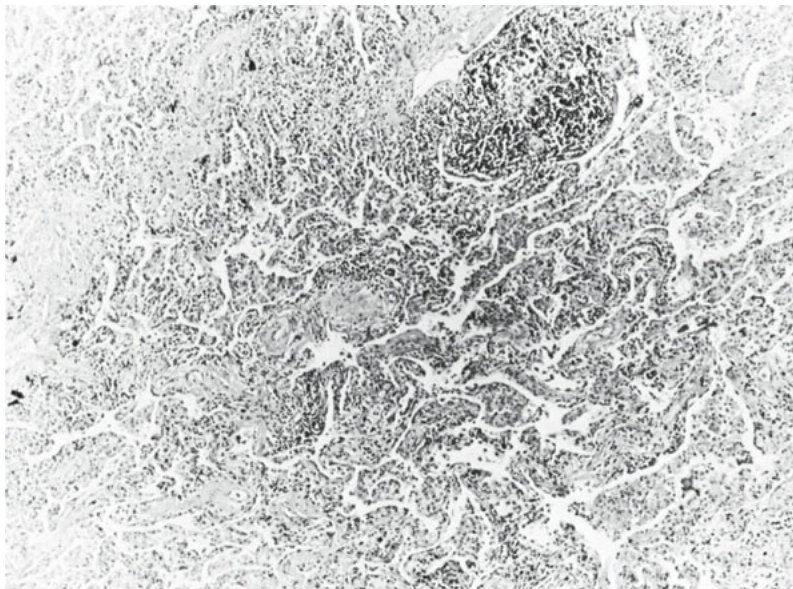
FIGURE 24.12 Typical microscopic appearance representing eosinophilic pneumonia. The collapsed alveolus contains a predominance of large mononuclear cells, few lymphocytes, plasma cells, and clumps of eosinophils; similar cells infiltrate the alveolar walls. Superior segment of the upper lobe was resected for a cavitary and infiltrative lesion. (Reprinted from Imbeau SA, Nichols D, Flaherty D, et al. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol*. 1978;62:243, with permission. Photographs from the specimen collection of Enrique Valdivia; magnification × 120, hematoxylin and eosin stain.)

PATHOGENESIS

On a historic basis, in some asthma patients who had a normal bronchogram before they developed ABPA, bronchiectasis has been found to occur at the sites of roentgenographic infiltrates. This phenomenon has been confirmed by repeated CT examinations as well. It is thought that inhaled spores grow in the patient's tenacious mucus and release antigenic glycoproteins and perhaps other reactants that activate bronchial mast cells, lymphocytes, macrophages, dendritic cells, and eosinophils, and generate antibodies, cytokines, and chemokines, followed by tissue damage that is associated with subsequent bronchiectasis or roentgenographic infiltrates. *Aspergillus* spores are thermophilic and aerobic; therefore, growth is feasible in bronchi. It is possible that spores are trapped in the viscid mucus, or alternatively, that they have a special ability (virulence) to colonize the bronchial tree and result in the development of tenacious mucus. The latter is such that during bronchoscopy, the mucoid material may remain impacted after 30 minutes of attempted removal. In contrast, in patients with CF without ABPA, such difficulty is not encountered. Proteolytic enzymes and presumably gliotoxins and ribotoxins produced by *A. fumigatus* growing in the bronchial tree may contribute to lung damage on a nonimmunologic or immunologic basis. Some strains of conidia of *A. fumigatus* have adhesive proteins that bind to fibrinogen, which itself functions as a substrate for the binding of pathogens to damaged epithelium and macrophages (127). It has been proposed that *Asp f 2* can bind to fibrinogen as well (102). Immunologic injury could occur because the release of antigenic material is associated with production of IgE, IgA, and IgG antibodies and activation of the pulmonary immune response with a panoply of harmful pro-inflammatory effects.
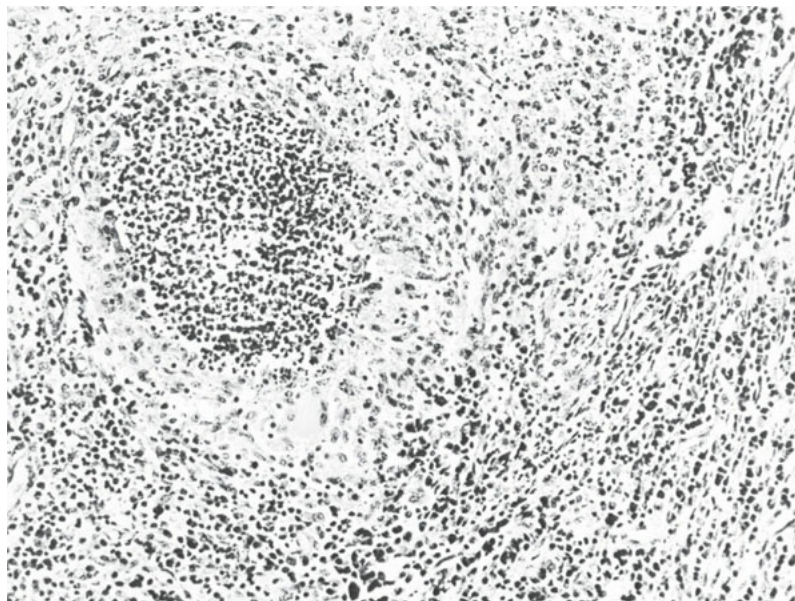
■ **FIGURE 24.13** Right lower lobectomy. The lung has prominent cellular

infiltration and an area of early bronchocentric granulomatosis, with leukocytes and a crown of epithelioid cells. *Aspergillus* was demonstrated in the center of the lesions with special stains. (Reprinted from Imbeau SA, Nichols D, Flaherty D, et al. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol*. 1978:62:243, with permission. Photographs from the specimen collection of Enrique Valdivia; magnification × 240, hematoxylin and eosin stain.)

Although peripheral blood lymphocytes from stable ABPA patients have not been reported to form excess IgE *in vitro* compared with nonatopic patients at the time of an ABPA flare-up, these cells produced significantly increased amounts of IgE (128). This suggests that during an ABPA flare-up, IgE-forming cells are released into the systemic circulation, presumably from the lung. The biphasic skin reaction requires IgE and, possibly, IgG, and it has been suggested that a similar reaction occurs in the lung. Nevertheless, the lack of immunofluorescence in vascular deposits is evidence against an immune complex vasculitis as a cause of bronchial wall damage.

Instructive experiments have been carried out in monkeys (129). The passive transfer of serum-containing IgG and IgE antibodies from a patient with ABPA to a monkey, followed by bronchial challenge with *A. fumigatus*, has been associated with pulmonary lesions in the monkey. First, monkeys were immunized with *A. fumigatus* and generated IgG antibodies. Then, *normal* human serum was infused into both immunized and nonimmunized monkeys, and *allergic* human serum from a patient with ABPA (currently without any precipitating antibody) was infused into other monkeys, immunized and nonimmunized (129). All animals were challenged with aerosolized *A. fumigatus*, and lung biopsy samples were obtained on the fifth day. Only the monkey with precipitating antibody (IgG) to *A. fumigatus* who received human allergic serum (IgE) showed biopsy changes consistent with ABPA (129). Mononuclear and eosinophilic infiltrates were present, with thickening of alveolar septa, but without evidence of vasculitis. These findings confirm that IgE and IgG directed against *A. fumigatus* are necessary for the development of pulmonary lesions.

Similarly, a murine model of ABPA was developed that resulted in blood and pulmonary eosinophilia using *A. fumigatus* particulates, which simulate spores (130). Intranasal inoculation of *A. fumigatus* particulates resulted in perivascular eosinophilia, as well as pulmonary lymphocytes, plasma cells, histocytes, and eosinophils consistent with ABPA. In contrast, if *A. fumigatus* in alum was injected into the peritoneal cavity, anti-*A. fumigatus*-IgG_1 and total IgE

concentrations increased, but pulmonary and peripheral blood eosinophilia did not occur. A true model of ABPA where animals develop spontaneously occurring pulmonary infiltrates has yet to be described.

It is established that CD4$^+$-T$_H$2 lymphocytes produce IL-4 (and IL-13) and IL-5 to support IgE synthesis and eosinophilia, respectively. Elevated soluble IL-2 receptors suggest CD4$^+$ lymphocyte activation (131), and CD4$^+$-T$_H$2 type clones have been produced from ABPA patients (82). The presentation of *Asp f* 1 is restricted to certain class II MHC molecules, HLA-DR2 and HLA-DR5 (82), and an increasing number of genetic susceptibilities have been described in preliminary studies (18). The demonstration of hyperreleasability of mediators from basophils of patients with stages IV and V ABPA (120) is consistent with the hypothesis that a subgroup of patients may be most susceptible to immunologic injury if peripheral blood basophils are representative bronchial mast cells. The fact that basophils from patients with any stage of ABPA have increased *in vitro* histamine release as compared with basophils from *A. fumigatus* skin-prick–positive patients with asthma suggests that mast cell mediator release to various antigens (fungi) may contribute to lung damage in ABPA if these findings can be applied to bronchial mast cells.

Analysis of bronchoalveolar lavage from stages II and IV ABPA patients who had no current chest roentgenographic infiltrates revealed evidence for local antibody production of IgA–*A. fumigatus* and IgE–*A. fumigatus* compared with peripheral blood (132). Bronchial lavage IgA–*A. fumigatus* was 96 times that of peripheral blood, and IgE–*A. fumigatus* in lavage was 48 times that found in peripheral blood. Although total serum IgE was elevated, there was no increase in bronchial lavage total IgE corrected for albumin. These results suggest that the bronchoalveolar space is not the source of the markedly elevated total IgE in ABPA (132). Perhaps pulmonary interstitium or nonpulmonary sources (tonsils or bone marrow) serve as sites of total IgE production in ABPA.

In a serial analysis of serum IgA–*A. fumigatus* in 10 patients, there were sharp elevations over baseline before (five cases) or during (five cases) roentgenographic exacerbations of ABPA for IgA$_1$–*A. fumigatus* (133). Serum IgA$_2$–*A. fumigatus* was elevated before the exacerbation in two cases and during the exacerbation in five cases. With immunoblotting of sera and staining with antibodies to IgE, IgA, and IgG, there were heterogeneous polyclonal antibody responses to seven different molecular weight bands of *A. fumigatus*. (133). Band intensity increased during ABPA exacerbations, and patient's sera often had broader reactivity with *A. fumigatus* bands from 24- to 90-kDa molecular

weights during disease flare-ups. Some patients had immunoblot patterns consistent with increases in IgE, IgG, or IgA antibodies binding to different *A. fumigatus* antigens but no consistent binding to a particular *A. fumigatus* band (133).

A summary of immunopathogenesis includes genetic susceptibility and powerful virulence factors, including proteases and enzymes from *A. fumigatus*, that can damage epithelium and interfere with surfactant, adhesive proteins, generation of tenacious eosinophil-rich mucoid impactions, a brisk CD4 T_H2 response with its characteristic cytokines and chemokines, activation of CD20 B cells and upregulation of CD23 (the low-affinity IgE receptor that binds allergen–IgE complexes) by IL-4, remarkable amounts of isotypic antibody production in the bronchoalveolar space and presumably interstitium, genetic restriction of HLA-DR2 and HLA-DR5 and gain of function polymorphisms for IL-4, eosinophil upregulation and activation, mast cell activation, basophil hyperreleasability and activation, and chemokines such as thymus- and activation-regulated chemokine and B-cell activating factor (134). The immunopathogenesis also includes allergic inflammation that is responsive to systemic but not inhaled corticosteroids and poorly responsive to intensive antifungal therapies.

■ DIFFERENTIAL DIAGNOSIS

The differential diagnosis of ABPA includes disease states associated primarily with transient or permanent roentgenographic lesions, asthma, peripheral blood or sputum eosinophilia, and increased total serum IgE concentration. The asthma patient with a roentgenographic infiltrate may have atelectasis or middle lobe collapse from inadequately controlled asthma. Bacterial, viral, or fungal pneumonias must be excluded in addition to *Mycobacterium tuberculosis* and the many other causes of roentgenographic infiltrates. Eosinophilia may occur with parasitism, *M. tuberculosis*, eosinophilic granulomatosis with polyangiitis, pulmonary infiltrates from drug allergies, neoplasm, eosinophilic pneumonia, and, rarely, avian-hypersensitivity pneumonitis. Mucoid impaction of bronchi may occur without ABPA. All patients with a history of mucoid impaction syndrome or with collapse of a lobe or lung, however, should have ABPA excluded. Similarly, although the morphologic diagnosis of bronchocentric granulomatosis is considered by some to represent an entity distinct from ABPA, ABPA must be excluded in such patients. Although the sweat test for CF is within normal limits in ABPA patients, unless concomitant CF is present, the patient with CF and asthma or changing roentgenographic infiltrates should have

ABPA excluded or confirmed. Genetic testing and assessment of pancreatic function for CF would be indicated. Some patients with asthma who develop pulmonary infiltrates with eosinophilia are likely to have ABPA or ABPM. Some patients will have mucus plugging (tree-in-bud) from atypical Mycobacteria (135).

In the patient without a history of roentgenographic infiltrates, ABPA should be suspected on the basis of (a) a positive, immediate cutaneous reaction to *A. fumigatus* or presence of *in vitro* anti-*A. fumigatus* IgE; (b) elevated total serum IgE (>417 kU/L); (c) increasing severity of asthma; (d) abnormalities on chest roentgenogram or CT; (e) repeatedly positive sputum cultures for *Aspergillus* species; or (f) bronchiectasis (14,15,18).

A rare patient with asthma, roentgenographic infiltrates, and bronchiectasis or a history of surgical resection for such may present with peripheral eosinophilia, elevated total serum IgE concentration, but other negative serologic results for ABPA. Some other species of *Aspergillus* may be responsible, such as *A. oryzae*, *Aspergillus ochraceus*, or *A. niger* (15,78). Perhaps a different ABPM may be present (15,78). For example, illnesses consistent with allergic bronchopulmonary candidiasis, curvulariosis, dreschleriosis, stemphyliosis, fusariosis, and pseudallescheriasis have been described (15,136–138). Positive sputum cultures, precipitating antibodies, or *in vitro* assays for a fungus other than *Aspergillus* or for different *Aspergillus* species could suggest a causative source of the ABPM.

The presence of bronchiectasis from ABPA has been associated with colonization of bronchi by nontuberculous mycobacteria (135). It appears that the identification of nontuberculous mycobacteria in the sputum of patients with asthma should at least raise the possibility of ABPA. Similarly, bronchiectatic airways may become colonized by *Pseudomonas aeruginosa* in ABPA patients who do not have CF.

NATURAL HISTORY

Although most patients are diagnosed before the age of 40 years, and an increasing number are diagnosed before the age of 20 years, one must not overlook the diagnosis of ABPA in older patients previously characterized as having persistent asthma or chronic bronchiectasis. Some patients as old as 80 have had the diagnosis of ABPA made. Late sequelae of ABPA include irreversible pulmonary function abnormalities, symptoms of chronic bronchitis, and pulmonary fibrosis (89,90). Death results from respiratory failure and cor

pulmonale (89,90). ABPA has been associated with respiratory failure in the second or third decade of life. Most patients who have ABPA do not progress to the end-stage disease, especially if there is early diagnosis and appropriate treatment. Patients who present in the acute stage (stage I) of ABPA may enter remission (stage II), recurrent exacerbation (stage III), or may develop corticosteroid-dependent asthma (stage IV). One patient who had a single roentgenographic infiltrate when her ABPA was diagnosed entered a remission stage that lasted for 8 years until an exacerbation occurred (139). Thus, a remission does not imply permanent cessation of disease activity. This patient may be the exception, but serves to emphasize the need for longer term observation of patients with ABPA. Patients who have corticosteroid-dependent asthma (stage IV) at the time of diagnosis may evolve into having pulmonary fibrosis (stage V). Because prednisone does not reverse bronchiectasis or the pulmonary fibrotic changes in the lung, every effort should be made by physicians and health care professionals managing patients with asthma to suspect and confirm cases of ABPA before significant structural damage to the lung has developed.

In managing patients with ABPA, there can be a lack of correlation between clinical symptoms and chest roentgenographic lesions. Irreversible lung damage, including bronchiectasis, may occur without the patient seeking medical attention. In Great Britain, ABPA exacerbations were reported to occur between October and February during elevations of fungal spore counts (45). In Chicago, 38 of 49 (77.5%) ABPA exacerbations (new roentgenographic infiltrate with elevation of total serum IgE concentration) occurred from June through November in association with increased outdoor fungal spore counts (140).

Acute and chronic pulmonary function changes have been studied in a series of ABPA cases, during which time all patients received corticosteroids and bronchodilators (141). There appeared to be no significant correlation between duration of ABPA (mean follow-up period, 44 months), duration of asthma, and diffusing capacity of the lungs for carbon monoxide, total lung capacity, vital capacity, forced expiratory volume in 1 second (FEV_1), and FEV_1%. In six patients with acute exacerbations of ABPA, a significant reduction in total lung capacity, vital capacity, FEV_1, and diffusing capacity of the lungs for carbon monoxide occurred, which returned to baseline during steroid treatment. Thus, early recognition and prompt effective treatment of flare-ups appear to reduce the likelihood of irreversible lung damage. Other patients may have reductions in FEV_1 and FEV_1% consistent with an obstructive process during an ABPA

exacerbation.

The prognosis for stage V patients is less favorable than for patients classified into stages I through IV (90). Although prednisone has proven useful in patients with end-stage lung disease, 6 of 17 stage V patients, observed for a mean 4.9 years, died. When the FEV_1 was 0.8 L or less after aggressive initial corticosteroid administration, the outcome was poor (90). In contrast, when stage IV patients are managed effectively, deterioration of respiratory function parameters or status asthmaticus has not occurred.

Prednisone remains the most effective treatment. Other treatments, including high-dose inhaled corticosteroids or antifungals (whether azoles or inhaled amphotericin), have not been more than adjunctive interventions. First published in 1973, from a 5-year follow-up of ABPA cases, it was reported that a daily prednisone dose of 7.5 mg was required to maintain clinical improvement and roentgenographic clearing in 80% of patients; of those treated with either cromolyn or bronchodilators alone, only 40% had radiologic clearing (142). In a study of patients from Northwestern University Feinberg School of Medicine, who had periodic blood sampling, both immunologic and clinical improvement occurred with prednisone therapy. Individuals with ABPA have high presentation (stages I and III) total serum IgE concentrations, and those patients previously never requiring oral steroids for control of asthma have the highest concentrations. Treatment with prednisone causes roentgenographic and clinical improvement, as well as decreases in total serum IgE. Total serum IgE and IgE–*A. fumigatus* may increase before and during a flare-up, but the serum IgE–*A. fumigatus* does not fluctuate to the extent that total serum IgE concentration does.

Prognostic factors remain to be established that may identify patients at risk for developing stage IV or V ABPA. The roentgenographic findings at the time of diagnosis do not appear to provide prognostic data about long-term outcome unless the patient is stage V. The effect of untreated ABPA exacerbations has produced stage V ABPA. In addition, at least some patients with CF who develop ABPA have a worse prognosis. Lastly, the effect of allergic fungal rhinosinusitis (Table 24.3) on the natural history of ABPA is unknown.

TREATMENT

Prednisone is the drug of choice but need not be administered indefinitely (Table 24.4). Multiple agents have been tried, including intrabronchial instillation of amphotericin B (143,144), oral nystatin (144), natamycin (144), azoles (144)

itraconazole, ketoconazole, voriconazole, and posaconazole, high-dose inhaled corticosteroids (145), and omalizumab (146–150). Itraconazole (151–155) or voriconazole or other antifungals may have an adjunctive role, but prednisone therapy typically eliminates or diminishes sputum plug production. Although the exact pathogenesis of ABPA is unknown, oral corticosteroids have been demonstrated to reduce the clinical symptoms, incidence of positive sputum cultures, and roentgenographic infiltrates. Oral corticosteroids may be effective by decreasing sputum volume, by making the bronchi a less suitable culture media for *Aspergillus* species, and by inhibiting many of the *Aspergillus*–pulmonary immune system interactions. The total serum IgE concentration declines by at least 35% within 2 months of initiating prednisone therapy (40). Failure to observe this reduction suggests noncompliance of patients or a continuing exacerbation of ABPA.

TABLE 24.3 CRITERIA FOR DIAGNOSIS OF ALLERGIC FUNGAL SINUSITIS

Chronic sinusitis—at least 6 mo duration with nasal polyposis

Allergic mucin (histologic examination with eosinophils and fungal hyphae and "putty" material by rhinoscopy)

Computed tomography of sinuses shows opacification, and magnetic resonance imaging shows fungal findings[a]

Absence of invasive fungal disease, diabetes mellitus, HIV

[a]T_1-weighted imaging reveals isointense or hypointense findings of mucin in sinuses; T_2-weighted imaging demonstrates a "signal void" where there is inspissated mucin.

TABLE 24.4 TREATMENT OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

1. Prednisone is drug of choice; 0.5 mg/kg daily for 2 wk, then on alternate days for 6–8 wk, then attempt tapering by 5 mg on alternate days every 2 wk.

2. Repeat chest roentgenogram and/or high-resolution computed tomography of lung at 2–4 wk to document clearing of infiltrates.

3. Serum IgE concentration at baseline and at 4 and 8 wk, then every 8 wk for first year to establish range of total IgE concentrations (a 100% increase can identify a silent exacerbation).

4. Baseline spirometry or full pulmonary function tests depending on the clinical setting.

5. Environmental control for fungi and other allergens at home or work.

6. Determine whether prednisone-dependent asthma (stage IV ABPA) is present; if not, manage asthma with anti-inflammatory medications and other medications as indicated.

7. Future ABPA exacerbations may be identified by

  a. Asymptomatic sharp increases in the total serum IgE concentration

  b. Increasing asthma symptoms or signs

  c. Deteriorations in FVC and/or FEV_1

  d. Cough, chest pain, new production of sputum plugs, dyspnea not explained by other causes

  e. Chest roentgenographic or high-resolution computed tomography findings (patient may be asymptomatic)

8. Document in record that prednisone side effects were discussed and address bone density issues (e.g., adequate calcium and vitamin D, exercise, and antiosteopenia medication if indicated).

9. Persistent sputum expectoration should be cultured to identify *Aspergillus fumigatus, Staphylococcus aureus, Pseudomonas aeruginosa*, nontuberculous mycobacteria, etc.

10. If new ABPA exacerbations occur, repeat step 1.

Our current treatment regimen is to clear the roentgenographic infiltrates with daily prednisone, usually at 0.5 mg/kg. Most infiltrates clear within 2 weeks, at which time the same dose, given on a single alternate-day regimen, is begun and maintained for 2 months until the total serum IgE, which should be followed up every 4 to 8 weeks for the first year, has reached a baseline concentration. The baseline total serum IgE concentration can remain elevated despite clinical and radiographic improvement. Slow reductions in prednisone, at no faster than 10 mg/month, can be initiated once a stable baseline of total IgE has been achieved. Acute exacerbations of ABPA are often preceded by a 100% increase in total serum IgE and must be treated promptly with increases in prednisone and reinstitution of daily steroids. Certainly, the physician must exclude other causes for roentgenographic infiltrates. Pulmonary functions should be measured yearly or as necessary for stages IV and V and as required for asthma.

If prednisone can be discontinued, the patient is in remission (stage II), and perhaps only an inhaled corticosteroid will be needed for management of asthma. Alternatively, if the patient has asthma that cannot be managed without prednisone despite avoidance measures and maximal anti-inflammatory medications, alternate-day prednisone will be necessary. The dose of prednisone required to control asthma and to prevent ABPA radiologic exacerbations is usually less than 0.5 mg/kg on alternate days. For corticosteroid-dependent patients (stage IV or V) with ABPA, an explanation of prednisone risks and benefits is indicated, as is the discussion that untreated ABPA infiltrates result in bronchiectasis and irreversible fibrosis. Specific additional recommendations regarding adequate calcium and vitamin D ingestion, bone density measurements, bronchial hygiene, and physical fitness should be considered.

In a two track study, the Northwestern regimen (prednisone 0.5 mg/kg/day for 2 weeks, then alternate days for 8 weeks; then reduce by 5 mg on alternate days every 2 weeks: discontinue after 3 to 5 months) was compared with a longer and initially higher course of daily prednisone (first 6 weeks 0.75 mg/kg/day, next 6 weeks, 0.5 mg/kg/day, taper by 5 mg every 6 weeks: discontinue after 8 to 10 months) (156). Both treatments were similar in clinical outcomes. The main difference was more side effects from oral corticosteroids in the latter arm (156).

In ABPA patients receiving prednisone, itraconazole, 200 mg twice daily or placebo, was administered for 16 weeks (151). A response was defined as (a) at

least a 50% reduction in oral corticosteroid dose and (b) a decrease of 25% or more of the total serum IgE concentration and at least one of three additional parameters: a 25% improvement in exercise tolerance or similar 25% improvement in pulmonary function tests or resolution of chest roentgenographic infiltrates if initially present with no subsequent new infiltrates, or if no initial chest roentgenographic infiltrates were present, no emergence of new infiltrates. Oral corticosteroids were tapered during the study, although it was not certain that all patients had an attempt at steroid tapering. With that consideration, itraconazole administration was associated with a response as defined. Unfortunately, less than 25% of patients had chest roentgenographic infiltrates at the beginning of the study. More responders (60%) occurred in patients without bronchiectasis (ABPA-S) versus ABPA-CB (31%), compared with 8% in placebo-treated patients (151). Eleven isolates from sputum cultures were analyzed for antifungal susceptibility, and five were susceptible to intraconazole (151). None of the patients whose isolates of *A. fumigatus* were resistant or intolerant *in vitro* to itraconazole had responses to treatment. The conclusions from this study were that patients with ABPA "generally benefit from concurrent itraconazole" (151). The difficulties and complexities in such studies are apparent, and ideally the drug would be of value in patients with ABPA-CB, who are the patients more frequently seen in the office. Itraconazole has anti-inflammatory effects and reduces eosinophils in induced sputum and lowers the total IgE concentration (154).

Itraconazole and posaconazole's absorption (but not voriconazole's) is reduced if there is gastric hypochlorhydria (157), so it should be ingested 1 hour before or 2 hours after meals. It slows hepatic metabolism of drugs that use the CYP 3A4 pathway, including methylprednisolone and dexamethasone (but not prednisolone), inhaled budesonide and fluticasone, statins, coumadin, oral hypoglycemics, tacrolimus, cyclosporines, and benzodiazepines, as examples. Itraconazole itself is potentiated by clarithromycin and some protease inhibitors used for human immunodeficiency virus infection. Voriconazole can cause skin rash/photosensitivity (not prevented by skin protection) (157).

Antifungal agents have been administered for 50 years to ABPA patients and are not a substitute for oral corticosteroids. Unfortunately, they remain adjunctive at best. The primary pharmacologic therapy remains prednisone, which, if the patient is in stage IV or V, often can be administered on an alternate-day basis. Perhaps itraconazole has anti-inflammatory effects or a delaying effect on corticosteroid elimination. If so, then its effects might resemble those of the macrolide troleandomycin, delaying the metabolism of

methylprednisolone. I have seen failures of itraconazole and voriconazole and excessive reliance on it without clearing of chest roentgenographic infiltrates. Nevertheless, as adjunctive therapy in patients who have susceptible strains of *A. fumigatus* or continue to produce mucus plugs despite prednisone, azoles can be considered in ABPA. Some studies have reported reductions in daily prednisone use and clearance of *A. fumigatus* from sputum.

In CF patients with ABPA, itraconazole was reported to result in a 47% reduction in oral steroid dose and a 55% reduction in ABPA exacerbations (29). The study group was composed of 16 patients (9%) from a pool of 122 CF patients. Itraconazole was administered to 12 of the 16 patients, who also received inhaled corticosteroids and prednisone and treatment for CF. Elevated serum aspartate aminotransferase or alanine aminotransferase results of greater than three times the upper limit of normal were contraindications to the use.

It has been thought that subcutaneous immunotherapy (SCIT) with *Aspergillus* species should not be administered in patients with ABPA, but examples of adverse effects aside from injection reactions have not been reported. It is known that SCIT with *Aspergillus* extracts would not result in immune complex formation. Immunotherapy can be administered with pollens and mites and other fungi, but not those in the *Aspergillus* genus. Nevertheless, this remains an area suitable for investigation, and inclusion of *Aspergillus* in the treatment is not absolutely contraindicated.

Inhaled corticosteroids should be used in an effort to control asthma, but one should not depend on them to prevent exacerbations of ABPA. Similarly, the leukotriene D_4 antagonists have antieosinophil actions *in vitro* and theoretically might be of value for use in ABPA patients. They can be administered for a trial of 1 to 3 months or continued for treatment of persistent asthma.

The immunobiologic omalizumab has potential benefit in treatment of patients with ABPA in asthma or CF (146–150). As with other treatments, if improvement (fewer exacerbations of asthma or reduction in prednisone) doesn't occur, the treatment should be discontinued after an initial trial of 6 to 12 months. There is no published information regarding the anti-IL-5 immunobiologics, mepolizumab and reslizumab, in ABPA. One could speculate that these treatments will be beneficial in treatment of patients with ABPA.

The exact role of environmental exposure of *Aspergillus* spores in the pathogenesis of ABPA remains unknown, primarily because of lack of firm evidence. Nevertheless, *Aspergillus* spores are found regularly in crawl spaces,

"unfinished" basements, compost piles, manure, and fertile soil. Some patients have developed acute wheezing dyspnea and recognized ABPA exacerbations after inhalation of heavy spore burdens such as moldy wood chips or after exposure to closed-up cottage homes. Attempts should be made to repair leaky basement walls and floors to minimize moldy basements. Because spores of *Aspergillus* species, including *A. fumigatus,* are detected regularly both indoors and outside, a common sense approach seems advisable.

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Occupational Immunologic Lung Disease and Occupational Rhinitis

LESLIE C. GRAMMER AND KATHLEEN E. HARRIS

■ INTRODUCTION

The most common immunologically mediated respiratory diseases caused by occupational exposure are occupational asthma (OA) and occupational rhinitis (OR) (1). High-molecular-weight (HMW) occupational agents can cause those diseases as well and hypersensitivity pneumonitis (HP) (2) which is covered in Chapter 23. Low-molecular-weight (LMW) agents, such as acid anhydrides, can cause OA, OR, and HP as well as less common occupational immunologic lung disease (OILD), such as pulmonary disease anemia syndrome and late respiratory systemic syndrome (Table 25.1).

■ DEFINITIONS

OA is one of two forms of work-related asthma (WRA) (3,4). The other form is work-exacerbated asthma in which the individual has preexisting asthma made worse by exposures in the workplace. OA can be subdivided into allergic or nonallergic, also called OA with or without latency, respectively (5). The most widely recognized nonallergic OA is reactive airways dysfunction syndrome (RADS) that occurs after a high-level irritant exposure to an agent, such as chlorine gas (Table 25.2). Allergic OA can be further subdivided into diseases caused by HMW agents that are mediated by immunoglobin E (IgE) and diseases caused by LMW agents that can be mediated by IgE, but other mechanisms also occur.

A parallel classification occurs with rhinitis. There is work-related rhinitis (WRR) that is comprised of work-exacerbated rhinitis and OR that can be allergic or nonallergic (6,7). Nonallergic OR has no latency and can occur with high exposure to an irritant-like ammonia gas, giving rise to reactive upper airway dysfunction syndrome. Allergic OR can be caused by HMW or LMW agents and is generally IgE mediated.

LWM agents can precipitate a disorder called work-associated irritable larynx

syndrome (WILS) that is characterized by chronic cough, laryngospasm, and globus (8). Along with WRR and WRA, WILS is a cause of cough in the workplace (9).

EPIDEMIOLOGY

The epidemiology of OILD and OR is difficult to assess for several reasons. First, there is often a high turnover rate in jobs associated with OILD and OR, thus selecting workers who have not become sensitized. In one study of an electronics industry, a substantial proportion of workers who left reported respiratory disease as the reason (10). Second, occupationally related diseases generally are underreported. For instance, although the incidence of work-related illness is thought to be upward of 20 per 100, only 2% of these illnesses were recorded in employers' logs, as required by the Occupational Safety and Health Administration (OSHA) (11). Finally, the incidence of disease varies with the antigen exposure involved. For example, the incidence of OA among animal handlers is estimated at 8%, whereas that of workers exposed to proteolytic enzymes can be up to 45% which is significantly higher (12). A recent literature review, primarily from Canada and Europe, suggests that the prevalence of OA may be decreasing (13).

TABLE 25.1 TRIMELLITIC ANHYDRIDE–INDUCED RESPIRATORY DISEASES AND IMMUNOLOGIC CORRELATES

DISEASE	MECHANISM	IMMUNOLOGIC TESTS
Asthma or rhinitis	IgE	Immediate skin test IgG against TM–protein conjugate
Late respiratory systemic syndrome	IgG and IgA	IgG, IgA, or total antibody against TM–protein conjugate
Pulmonary disease, anemia syndrome	Complement-fixing antibodies	Complement-fixing antibodies against TM cells

IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; TM, trimellityl.

TABLE 25.2 CRITERIA FOR REACTIVE AIRWAYS DYSFUNCTION SYNDROME

1. No history of bronchospastic respiratory disease

2. Onset of symptoms follows a high-level exposure to a respiratory irritant

3. Onset of symptoms is abrupt, within minutes to hours

4. Symptoms must persist for at least 3 mo

5. Methacholine challenge is positive

6. The symptoms are asthma like, such as cough and wheeze

7. Other respiratory disorders have been excluded

It has been estimated that 2% of all cases of asthma in industrialized nations are occupationally related. In US surveys, 9% to 15% of adult asthma cases were classified as occupational in origin. The European Community Respiratory Health Survey Study Group reported the highest risk for asthma was in farmers (odds ratio, 2.62), painters (2.34), plastic workers (2.20), cleaners (1.97), and spray painters (1.96) (14). In one American study of WRA in California, Massachusetts, Michigan, and New Jersey, the most common industries where OA occurred were transportation manufacturing equipment (19.3%), health services (14.2%), and educational services (8.7%) (15).

MEDICOLEGAL ASPECTS

Most sensitizing agents that have been reported to cause OA are proteins of plant, animal, or microbial derivation and are, therefore, not specifically regulated by OSHA. Some of the LMW sensitizers, such as isocyanates, anhydrides, and platinum, are regulated by OSHA; published standards for airborne exposure can be found in the Code of Federal Regulations (CFR 29.1927-1999) (16). OSHA, a division of the US Department of Labor, is responsible for determining and enforcing these legal standards. The National Institute of Occupational Health and Safety, a division of the US Department of

Health and Human Services, is responsible for reviewing available research data on exposure to hazardous agents and providing recommendations to OSHA, but has no regulatory or enforcement authority. More than 400 different substances have been reported to act as respiratory sensitizers and causes of OA and OR, and new sensitizers continue to be reported (17).

The Hazard Communication Standard, also called "worker right-to-know" legislation at the federal, state, and local levels, was passed in the United States about four decades ago (18). Substances that are capable of inducing respiratory sensitization are generally considered hazardous, and thus workers exposed to such substances are covered in most legislation. The common elements that exist in most hazard communication legislation are (a) that the employer apprise a governmental agency relative to its use of hazardous substances; (b) that the employer inform the employee of the availability of information on hazardous substances to which the employee is exposed; (c) that alphabetized material safety data sheets for hazardous substances in the workplace be available to the employee; (d) that there be labeling of containers of hazardous substances; and (e) that training be provided to employees relative to health hazards, methods of detection, and protective measures to be used in handling hazardous substances. This hazard communication legislation may make workers more aware of the potential that exists to develop respiratory sensitization and OR or OILD syndromes as a result of certain exposures.

Legal and ethical aspects of management of individuals with OA are major problems. Guidelines for assessing impairment and disability from OA continue to evolve (19,20). The American Thoracic Society has proposed criteria based on a possible four points for each of the following: forced expiratory volume in 1 second, methacholine challenge, and medication. After totaling the points, the degree of impairment can be determined (20). Depending on the occupation, disability can then be assessed.

OCCUPATIONAL ASTHMA AND RHINITIS

Pathophysiology

The pathophysiology of asthma and rhinitis is reviewed in Chapters 19 and 26. The major pathophysiologic abnormalities of asthma, occupational, or otherwise, are bronchoconstriction, excess mucus production, and bronchial wall inflammatory infiltration, including activated T cells, mast cells, and eosinophils. Neutrophilic OA has also been described (21). There is evidence that these abnormalities may be at least in part explained by neurogenic mechanisms and

release of inflammatory mediators and cytokines, such as interleukins and interferons. Type I hypersensitivity involving cross-linking of IgE on the surface of mast cells and basophils, resulting in release of mediators such as histamine and leukotrienes, is believed to be the triggering mechanism in most types of immediate-onset asthma and rhinitis. There is increasing evidence that cellular mechanisms are very important in asthma, especially in delayed types (21). An updated paradigm of the Gell and Coombs classification is improving our understanding of some of those cellular mechanisms (22). There are now four types of type IV, or cellular, mechanisms, including type IV_{a2}, which involves T_H2 cells and is probably responsible for late asthmatic responses.

Reaction Patterns

A number of patterns of asthma may occur after a single inhalation challenge, as shown in Table 25.3 (3,4). The immediate reaction is mediated by IgE, occurs within minutes of challenge, presents as large airway obstruction, and is preventable with cromolyn and reversible by bronchodilators. The late response occurs several hours after inhalation challenge, presents as small airway obstruction in which wheezing may be mild and cough and dyspnea may predominate, lasts for several hours, is usually preventable with steroids (23) or cromolyn, and is only partly reversed by most bronchodilators.

The dual response is a combination of the immediate and late asthmatic responses. It is partially prevented by steroids or bronchodilators. After a single challenge study with certain antigens like Western red cedar, the patient may have repetitive asthmatic responses occurring over several days. This repetitive asthmatic response can be reversed with bronchodilators. Other atypical patterns —square wave, progressive, and progressive and prolonged immediate—have been described after diisocyanate challenges; the mechanisms resulting in these patterns have not been elucidated (24).

Etiologic Agents

Most of the 400 agents that have been described to cause OA and OR are HMW (>1 kDa) heterologous proteins of plant, animal, or microbial origin. LMW chemicals can act as irritants and aggravate preexisting asthma. They may also act as allergens if they are capable of haptenizing autologous proteins in the respiratory tract. Numerous reviews of OA have information on etiologic agents (25,26). A representative list of agents and industries associated with OILD can be found in Table 25.4.

TABLE 25.3 TYPES OF RESPIRATORY RESPONSE TO INHALATION CHALLENGE

ASTHMA	IMMEDIATE	LATE	REPETITIVE
Onset	10–20 min	4–6 h	Periodic after initial attack
Duration	1–2 h	2–6 h	Days
Abnormality	FEV_1	FEV_1	FEV_1
Immune mechanism	Type I (IgE)	Type IV_{a2}	Type IVb CD8?
Symptoms	Wheezing	Wheezing, dyspnea	Recurrent wheezing
Therapy	Bronchodilators	Bronchodilators, corticosteroids	Bronchodilators

FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IgG, immunoglobulin G.

Etiologic Agents of Animal Origin

Proteolytic enzymes are known to cause asthmatic symptoms on the basis of type I immediate hypersensitivity. Examples are pancreatic enzymes, hog trypsin used in the manufacture of plastic polymer resins, *Bacillus subtilis* enzymes (27) incorporated into laundry detergents, and subtilisin. Papain, which is a proteolytic enzyme of vegetable origin used in brewing beer and manufacturing meat tenderizer, has been noted to cause similar symptoms by IgE-mediated mechanisms (28). Several enzymes have been described as new causes of OA and OR: savinase, a genetically engineered amylase, and a microbial transglutaminase (17).

TABLE 25.4 EXAMPLES OF OCCUPATIONAL ALLERGENS	
AGENT	INDUSTRIES AND OCCUPATIONS

Animal Proteins	
Proteolytic enzymes	Detergent industry; pharmaceutic industry; meat tenderizer manufacturing; beer clearing
Animal dander, saliva, urine	Lab researchers; veterinarians; grooms; breeders; pet shop owners; farmers
Avian protein	Poultry breeders; bird fanciers; egg processors
Insect scales	Beekeepers; insect control workers; bait handlers; mushroom workers; entomologists

Vegetable Proteins	
Latex	Health care workers
Flour or contaminants (insects, molds)	Bakers
Green coffee beans, tea, garlic, other spices, soybeans	Workers in processing plants
Grain dust	Farmers; workers in processing plants
Castor beans	Fertilizer workers
Guar gum	Carpet manufacturing
Wood dusts: boxwood, mahogany, oak, redwood, Western red cedar	Carpenters; sawyers, wood pulp workers; foresters; cabinet makers

Penicillium caseii	Cheese workers
Orris root, rice flour	Hairdressers
Thermophilic molds	Mushroom workers
Chemicals	
Antibiotics	Hospital and pharmaceutic personnel
Other drugs; piperazine hydrochloride, α-methyldopa, amprolium hydrochloride	Hospital and pharmaceutic personnel
Platinum	Workers in processing plants; production of cisplatin
Nickel chromium, cobalt, and zinc	Workers using those metals
Anhydrides (TMA, PA, TCPA)	Workers in manufacture of curing agents, plasticizers, anticorrosive coatings
Azo dyes	Dye manufacturers
Ethylenediamine	Shellac and lacquer industry workers
Isocyanates	Production of paints, surface coatings, insulation polyurethane foam
Soldering fluxes, colophony	Welders
Chloramine-T	Sterilization

PA, phthalic anhydride; TCPA, tetrachlorophthalic anhydride; TMA, trimellitic anhydride.

Animal dander can cause asthma in a variety of workers, including veterinarians, laboratory workers, grooms, shepherds, breeders, pet shop owners, farmers, and jockeys (3,4). This can even be a problem for people whose work takes them to homes of clients who have pets, such as real estate agents, interior designers, and domestic workers.

Immediate asthmatic reactions and late interstitial responses have been reported after inhalation challenge with avian proteins in people who raise poultry and in workers exposed to egg products in egg processing facilities. Positive skin test results and *in vitro* IgE antibody have been demonstrated as well (3,4).

A variety of insect scales have been associated with asthma. Occupational exposure to insect scales occurs in numerous circumstances (3,4). Bait handlers can become sensitized to mealworms used as fishing bait. Positive skin test results, *in vitro* IgE antibody, and positive inhalation challenges have been demonstrated to mealworms. Positive skin test results have been shown in various workers who have asthma upon insect exposure to screw worm flies in insect control personnel, to moths in fish bait workers, and to weevils in grain dust workers.

Asthma has been reported in workers who crush oyster shells to remove the meat. On the basis of skin tests to various allergens, the authors determined that the allergen was actually the primitive organisms that attached to the oyster shell surface. Similarly, asthma may occur from sea squirt body fluids in workers who gather pearls and oysters and in snow crab workers (29).

Etiologic Agents of Vegetable Origin

In terms of plant protein antigens, exposure to latex antigens, particularly those dispersed by powder in exam gloves, has become an important cause of OA in the health care setting. People working in a number of other occupations, including seamstresses, may develop latex hypersensitivity (30). In the baking industry, flour proteins are well recognized to cause OA (31). Numerous other plant foodstuff proteins, including tea, garlic, coffee beans, spices, soybeans, vegetable gums, castor bean, guar gum, grain dust, wood dust, and dried flowers, have been described to cause OA (3,4). In addition to the plant-derived proteins enumerated above, a variety of microbial proteins have been reported to be sensitizing agents in OA, including those from *Alternaria, Aspergillus,* and *Cladisporium* species (3,4). Wood dust from Western red cedar is a well recognized cause of OA, but the antigen appears to be the LMW chemical, plicatic acid, not an HMW plant protein (32).

Chemicals

Asthma has been described in pharmaceutic workers and hospital personnel exposed to pharmacologic products. Numerous antibiotics, including ampicillin, penicillin, spiramycin, and sulfas (3,4), are known to cause asthma, positive skin test results, and/or specific IgE antibody. Other pharmaceutic, including amprolium hydrochloride, α-methyldopa, and piperazine hydrochloride, have been reported to cause asthma on an immunologic basis.

Workers in platinum-processing plants may have rhinitis, conjunctivitis, and asthma (33). Positive bronchial challenges and specific IgE have been demonstrated in affected workers. Another metal, nickel sulfate, has also been reported to cause IgE-mediated asthma (34). Other metals reported to cause OA and OR include chromium, cobalt, vanadium, and zinc (3,4).

The manufacture of epoxy resins requires a curing agent, usually an acid anhydride or a polyamine compound. Workers may thus be exposed to acid anhydrides in the manufacture of curing agents, plasticizers, and anticorrosive coating materials. Studies have reported that three different patterns of immunologic respiratory response may occur (Table 25.1).

Initially, it was presumed that the antibody in affected workers was directed only against the trimellityl (TM) haptenic determinant. However, studies of antibody specificity have demonstrated that there is antibody directed against both hapten and TM–protein determinants that are considered new antigen determinants. Other acid anhydrides that have been described to cause similar respiratory hypersensitivity reactions include phthalic anhydride (PA), hexahydrophthalic anhydride (HHPA), and maleic anhydride (3,4). HHPA has also been described to cause hemorrhagic rhinitis via an immunologic mechanism (35).

Isocyanates are required catalysts in the production of polyurethane foam, vehicle spray paint, and protective surface coatings. It is estimated that about 5% to 10% of isocyanate workers develop asthma from exposure to subtoxic levels after a variable period of latency (36). The isocyanates that have been described to cause OA include toluylene diisocyanate, hexamethylene diisocyanate, and diphenylmethyl diisocyanate (36). The histology of bronchial biopsy specimens from workers with isocyanate asthma appears very similar to that from patients with immunologic asthma and thus is suggestive of an immunologic mechanism. Compared with those isocyanate workers with negative bronchial challenges, workers with positive challenges have a higher prevalence and level of antibody against isocyanate–protein conjugates. However, in most studies, isocyanate

workers with positive challenges did not have detectable specific IgE in their serum. In one study, it is speculated that some isocyanate asthma is mediated by IgE, but more than half is not (37). HP (38) and hemorrhagic pneumonitis (39) as a result of isocyanates have been reported to be caused by immunologic mechanisms.

Formaldehyde, a respiratory irritant at ambient concentrations of 1 ppm or more, is sometimes cited as a cause of OA; however, documented instances of formaldehyde-induced IgE-mediated asthma are almost nonexistent (40). A bifunctional aldehyde, glutaraldehyde, has been reported to cause OA (41). Ethylenediamine, a chemical used in shellac and photographic developing industries, has been reported to cause OA and OR (42). Chloramine T (43), reactive azo dyes (44), and dimethyl ethanolamine are other chemicals that have also been reported to be causes of OA (45).

HYPERSENSITIVITY PNEUMONITIS

The signs, symptoms, immunologic features, pulmonary function abnormalities, pathology, and laboratory findings of HP are reviewed in Chapter 23. No matter what the etiologic agent, the presentation follows one of three patterns. In the acute form, patients have fever, chills, chest tightness, dyspnea without wheezing, and nonproductive cough 4 to 8 hours after exposure. The acute form resolves within 24 hours. In the chronic form, which results from prolonged low-level exposure, patients have mild coughing, dyspnea, fatigue, pulmonary fibrosis, and weight loss. There is also a subacute form, which presents as a clinical syndrome of productive cough, malaise, myalgias, dyspnea, and nodular infiltrates on chest film. Any form can lead to severe pulmonary fibrosis with irreversible change; thus, it is important to recognize this disease early so that significant irreversible lung damage does not occur.

A variety of organic dusts from fungal, bacterial, or serum protein sources in occupational settings have been identified as etiologic agents of HP (2) (Table 25.5). Several chemicals, including anhydrides and isocyanates, as discussed previously, have been reported to cause HP; others include organochlorine and carbamate pesticides (2).

DIAGNOSIS

The diagnosis of OILD is not difficult in the individual worker if symptoms appear at the workplace shortly after exposure to a well-recognized antigen. However, the diagnosis can be challenging in patients whose symptoms occur

many hours after exposure, for instance, late asthma from trimellitic anhydride. Because of the increasing importance of OILD, it has become essential to evaluate patients with respiratory syndromes for a possible association between their disease states, their pulmonary function test results, and their exposures in the work environment. In some cases, rhinoconjunctivitis precedes OA (46,47).

In the case of a well-established OILD syndrome, a careful history and physical examination with corroborative immunology and spirometry will suffice (3). The history and physical examination findings in asthma, rhinitis, and HP are discussed in Chapters 19, 26, and 23. Immunologic evaluations may provide important information about the cause of the respiratory disease. Skin tests, with antigens determined to be present in the environment, may detect IgE antibodies and suggest a causal relationship (3). Haptens may be coupled to carrier proteins, such as human serum albumin, and used in skin tests (45) or immunoassays. In cases of HP, double gel immunodiffusion techniques may be used to determine the presence of precipitating antibody, which would indicate antibody production against antigens known to cause disease (2).

It may be necessary to attempt to reproduce the clinical features of asthma or interstitial lung disease by bronchial challenge, followed by careful observation of the worker. Challenge may be conducted by natural exposure of the patient to the work environment with pre- and postexposure pulmonary functions, compared with similar studies on nonwork days. Another technique used for diagnosis of OILD is controlled bronchoprovocation in the laboratory with pre- and postexposure pulmonary function measurements (3,48). It is important that the intensity of exposure not exceed that ordinarily encountered on the job and that appropriate personnel and equipment be available to treat respiratory abnormalities that may occur. Some advocate the use of peak flow monitoring, whereas others find it less reliable (3). Evaluating induced sputum eosinophils has been reported to be a potentially useful technique to diagnose OA (49).

TABLE 25.5 OCCUPATIONAL HYPERSENSITIVITY PNEUMONITIDES

DISEASE	EXPOSURE	SPECIFIC INHALANT
Farmer's lung	Moldy hay	*Saccharopolyspora rectivirgula*
		Thermoactinomyces vulgaris

Malt worker's disease	Fungal spores	*Aspergillus clavatus*
		Aspergillus fumigatus
Maple-bark stripper's disease	Moldy logs	*Cryptostroma corticale*
Wood pulp worker's disease	Moldy logs	*Alternaria* and *Rhizopus* species
Sequoiosis	Moldy redwood sawdust	*Graphium* species; *Aureobasidium pullulans*
Suberosis (cork worker's lung)	Moldy cork	*Penicillium glabrum, Chrysonilia sitophila, A. fumigatus*
Humidifier/air conditioner disease	Fungal spores	Thermophilic actinomycetes
		Naegleria gruberi
Bird breeder's disease	Avian dust	Avian serum
Bagassosis	Moldy sugarcane	*Thermoactinomyces vulgaris*
Mushroom worker's disease	Mushroom compost	*S. rectivirgula*
		T. vulgaris
Isocyanate disease	Isocyanates	Toluene diisocyanate
		Diphenylmethane diisocyanate
Metal worker's lung	Contaminated metal working fluid	*Mycobacterium immunogen*
Cheese worker's lung	Mold used in cheese production	*Penicillium roqueforti*

If the analysis of OILD is not for an individual patient but rather for a group of workers afflicted with a respiratory illness, the approach is somewhat different. The initial approach to an epidemiologic evaluation of OILD is usually a cross-sectional survey using a well-designed questionnaire (50). The questionnaire should include a chronologic description of all past job exposures, symptoms, chemical exposures and levels, length of employment, and protective respiratory equipment used. Analysis of the survey can establish possible sources of exposure. All known information about the sources of exposure should be sought in the form of previously reported toxic or immunologic reactions. Ultimately, immunologic tests and challenges may be done selectively.

PROGNOSIS

Unfortunately, many workers with OA do not completely recover, even though they have been removed from exposure to a sensitizing agent (4,51). Prognostic factors that been examined include specific IgE, duration of symptoms, pulmonary function testing, and nonspecific bronchial hyperreactivity (BHR). An unfavorable prognosis has been reported to be associated with a persistent high level of specific IgE, long duration of symptoms (>1 to 2 years), abnormal pulmonary function test results, and a high degree of BHR (51). The obvious conclusion from these studies is that early diagnosis and removal from exposure are requisites for the goal of complete recovery. In workers who remain exposed after a diagnosis of OA is made, further deterioration of lung function and increase in BHR have been reported (4). It must be appreciated that life-threatening attacks and even deaths have been reported when exposure continued after diagnosis (3,4).

TREATMENT

The management of OILD consists of controlling the worker's exposure to the offending agent. This can be accomplished in various ways. Sometimes, the worker can be moved to another station; efficient dust and vapor extraction can be instituted; or the ventilation can be improved in other ways, so that a total job change is not required (52). Consultation with an industrial hygienist familiar with exposure levels may be helpful in this regard. It is important to remember that the levels of exposure below the legal limits that are based on toxicity may still cause immunologic reactions. Face masks of the filtering type are not especially efficient or well tolerated. Ideally, the working environment should be designed to limit the concentration of potential sensitizers to safe levels. Thus, avoidance may well entail retraining and reassigning an employee to another job

(53).

Pharmacologic management of OILD is rarely helpful in the presence of continued exposure. Certainly, in acute HP, a short course of oral corticosteroids is useful in conjunction with avoidance. However, chronic administration of steroids for occupational HP is not recommended. Asthma resulting from contact with occupational exposures responds to therapeutic agents, such as β-adrenergic receptor agonists, leukotriene modifiers, and inhaled and oral corticosteroids. As exposure continues, sensitivity may increase, thereby making medication requirements prohibitive.

Immunotherapy has been used with various occupational allergens causing asthma, including treatment of laboratory animal workers, bakers, and oyster gatherers, with reported success. To date, there are no double-blind placebo-controlled trials. Immunotherapy may be feasible in rare cases, with certain occupational allergens of the same nature as the common inhalant allergens.

PREVENTION

The key principle in OILD is that prevention, rather than treatment, must be the goal (54). Such preventative measures as improved ventilation and adhering to threshold limits, as discussed under section "Treatment," would be helpful to this end. There should be efforts to educate individual workers and managers in high-risk industries so that affected workers can be recognized early.

Currently, there are no preemployment screening criteria that have been shown to be useful in predicting the eventual appearance of OILD. There is conflicting evidence as to whether HLA studies are useful in predicting isocyanate asthma or anhydride asthma. It has been reported that atopy is a predisposing factor for a worker to develop IgE-mediated disease (46), but there is at least one conflicting study (55). Whether or not cigarette smoking is a risk factor for OILD is unclear.

Prospective studies of acid anhydride workers, such as those of Zeiss et al. (56), Baur et al. (57), and Newman-Taylor et al. (58), have reported that serial immunologic studies are useful in predicting which workers are likely to develop immunologically mediated diseases. At the first sign of OA, those workers then could be removed from the offending exposure and retrained before permanent illness develops. Multiple studies have reported that decreasing the airborne levels will reduce disease prevalence (54). This appears to be the best approach to preventing OILD and OR. In one study, medical surveillance studies with cost–benefit analyses have been reported to reduce cases of permanent OA (59).

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Upper Respiratory Tract Diseases

Allergic Rhinitis
PETER A. RICKETTI AND ANTHONY J. RICKETTI

■ INTRODUCTION AND DEFINITIONS

The clinical definition of allergic rhinitis (AR) is a symptomatic disorder of the nose induced by an immunoglobulin E (IgE)-mediated inflammatory reaction after allergen exposure of the membranes lining the nose (1). The symptoms that characterize the disorder are rhinorrhea, nasal congestion, sneezing, nasal pruritus, postnasal drainage, and, at times, pruritus of the eyes, ears, and throat. General symptoms such as fatigue, impaired concentration, and reduced productivity are also associated with AR.

Previously, AR was subdivided, based on the time of exposure into either a seasonal or a perennial disorder. Perennial allergic rhinitis (PAR) is the most frequently caused by indoor allergens, such as dust mites, mold spores, animal dander, and cockroaches. Seasonal allergic rhinitis (SAR) is related to a wide variety of pollens and molds. However, it became evident that a new classification system was required because of several clinical observations (2):

- In many areas of the world, pollens and molds are perennial allergens (e.g., the weed *Parietaria* pollen allergy in the Mediterranean area (3) and grass pollen allergy in southern California and Florida) (4).

- Symptoms of PAR may not always be present throughout the year.

- Many patients who are sensitive to pollen and also allergic to mold may have difficulty defining a pollen season (5).

- The majority of patients are sensitized to several allergens and, therefore, manifest symptoms not only seasonally but throughout the year (6).

The priming effect on the nasal mucosa induced by low levels of pollen allergens (7) and persistent inflammation of the nose in asymptomatic AR patients may result in rhinitis symptoms not confined to the specific allergy season (8).

The 2012 AR and its Impact on Asthma workshop guidelines for the classification and treatment of AR (2) have led to the definitions of allergic nasal disease as intermittent or persistent, and mild or moderate-severe category (2). Intermittent rhinitis is defined on the basis of symptoms that are present for fewer than 4 days/week or fewer than 4 weeks (2). When symptoms are present for more than 4 days/week and are present for more than 4 weeks, it is defined as persistent rhinitis. Mild symptoms do not affect sleep, impair participation in daily activities, sports, and leisure, or interfere with work or school and are not considered bothersome (2). Conversely, moderate-severe symptoms result in abnormal sleep, interfere with daily activities, sports, and leisure, impair work and school activities, and are considered troublesome. Any one of the designators classifies AR into the moderate-severe category (2).

EPIDEMIOLOGY

Although AR may have its onset at any age, the incidence of onset is greatest in children at adolescence, with a decrease in incidence seen in advancing age. It effects up to 60 million people in the United States annually. Up to 30% of adults and up to 40% of children self-report AR (9). Surveys which require a physician-confirmed diagnosis of AR report a 14% prevalence in US adults, 13% of children, 7% of Latin American adults, and 9% of Asian-Pacific adults (10). Although it has been reported in infants (10), in most cases, an individual requires two or more seasons of exposure to a new antigen before exhibiting the clinical manifestations of AR. Children with a bilateral family history of atopy may develop symptoms more frequently and at a younger age than those with a unilateral family history (11,12). Infants born to atopic families are sensitized to pollen aeroallergens more frequently than indoor aeroallergens in the first year of life (13).

The prevalence of SAR is higher in children and adolescents, whereas PAR has a higher prevalence in adults (14). Older children have a higher prevalence of AR than younger ones, with a peak occurring in children aged 13 to 14 years. Approximately 80% of individuals diagnosed with AR will develop symptoms before the age of 20 years (15). Boys tend to have an increased incidence of AR in childhood, but females are more commonly affected in adulthood.

Epidemiology studies suggest that the prevalence of AR in the United States and around the world is increasing and more than 40% in many populations in the United States and Europe (16). However, accurate estimates of AR are difficult to obtain secondary to variability of geographic pollen counts, misinterpretation of symptoms by patients, and inability of the patient and physician to recognize the disorder. Climate change has resulted in a change in the duration of allergy seasons and the geographic pollen counts during different seasons. Although there is an increased prevalence of AR, the cause for this increase is unknown. Risk factors associated with development of AR include family history, (17) higher socioeconomic status (18), atmospheric pollution (19), ethnicity other than white (20), late entry into daycare (21), lack of other siblings (22), birth during a pollen season (23), heavy maternal smoking during the first year of life (24), exposure to high concentrations of indoor allergens, such as mold spores, dust mites, and animal dander (25), higher serum IgE (>100 IU/mL before the age of 6 years) (24), the presence of positive allergen skin-prick tests (26), early introduction of foods or formula (24), and a trend toward sedentary lifestyles (27).

Burden of Disease

According to 1997 survey data from primary care physicians, there were 16.9 million office visits for symptoms suggestive of AR (28). In 2000, more than $6 billion was spent on prescription medications for this condition, and over-the-counter medications were at least twice that amount (29). Compared with matched controls, patients with AR have an approximately twofold increase in medication costs and a 1.8-fold increase in the number of visits to a health care practitioner (30). In Europe, the total societal cost of persistent AR and its comorbidities in 2002 were estimated at €355.05 per patient month (31). Employer and societal costs may be substantially reduced with appropriate therapy of AR. Unfortunately, the lack of treatment, undertreatment, and nonadherence to treatment has been shown to increase direct and indirect costs (32). In addition to the characteristic nasal and ocular symptoms of AR, patients can experience fatigue, headache, disrupted sleep patterns, and declines in

cognitive processing, psychomotor speed, verbal learning, and memory (33). Hidden direct costs include the treatment of asthma, upper respiratory infection, chronic sinusitis, otitis media, nasal polyposis, and obstructive sleep apnea (34). Surveys report that 38% of patients with AR have coexisting asthma, and as many as 78% of patients with asthma also have AR (35). Asthma and AR are often thought of as conditions that characterize different points on a continuum of inflammation within one common airway (36). Evidence suggests a common pathophysiology for these allergen-induced disorders and supports the observation that treatment of AR reduces the incidence and severity of asthma (37). Asthma patients with AR experience incomplete asthma control and have higher medical resource use, including acute asthma exacerbations, emergency department visits, unscheduled physician office visits, and prescription medication use when compared to asthma patients without concomitant AR (38–40). Allergy has been linked as a contributing factor in 40% to 80% of cases of chronic rhinosinusitis (41). Approximately 21% of children with nasal allergies experience otitis media with effusion (OME). Children with an OME have a 35% to 50% incidence of allergy (42,43). In patients with AR, an allergen challenge induces expression of intercellular adhesion molecule 1 (ICAM-1), the receptor for 90% of human rhinoviruses (41), thus increasing the susceptibility for an upper respiratory infection. In turn, rhinovirus can accentuate the pattern of airway reactivity in patients with AR (44). Although the link between AR and nasal polyps does not appear to be causal, the recurrence rate of nasal polyps in patients with AR is higher than for patients who are nonallergic (45). The indirect costs of AR, such as absenteeism and presenteeism (decreased productivity while at work), are also substantial. AR results in impaired productivity and/or missed work in 52% of patients (46). In a survey of 8,267 US employees, 55% experienced AR symptoms for an average of 52.5 days, were absent from work for 3.6 days/year because of their condition, and were unproductive 2.3 hours/work day when experiencing symptoms. The mean total productivity (absenteeism and presenteeism) losses were $593 per employee per year (47). In total, AR results in an estimated 3.5 million lost work days and 2 million lost school days (32). Approximately 10,000 children are absent from school on any given day secondary to AR (32). Depending on a child's age, absence from school may also affect parents' productivity or absence from work.

The impact of AR on patient-perceived health status is substantial. When compared to patients without AR, nearly twice as many AR patients rated their health as only fair/poor/very poor. Almost twice as many patients with AR compared with adults without nasal allergies say that their health limited them in

daytime physical indoor activities and outdoor activities (48). In one Spanish study, the negative impact on daily activities for patients with AR was greater than for patients with type 2 diabetes mellitus and hypertension (49). Patient evaluations of disease severity have shown that patients rate their disease more persistent and severe than physicians (50). Quality of life surveys have evaluated the impairment secondary to AR. In the Medical Outcomes Study Short-Form Health Survey, of 36 items administered to patients with AR and asthma (51), patients with AR had similar impairment with asthma when evaluating energy/fatigue, general health perception, physical role limitations as well as emotional role limitations—mental health, pain, and change in health. Patients with AR actually had significantly lower scores than asthma patients in the area of social functioning. These surveys clearly demonstrate the overall morbidity of the disorder, and therefore, the symptoms of these patients should not be trivialized.

GENETICS

The development of AR entails a complex interaction between environmental exposure and genetic predisposition to implicated allergens. The hereditary nature of AR and other atopic diseases has been frequently demonstrated in families and twins (52). In a series of 8,633 of 5-year old twins in which the prevalence of rhinitis was 4.4%, there was a 93% correlation in full-term monozygotic twins and a 53% correlation in dizygotic twins having rhinitis. Atopy has also been linked to multiple genetic loci on chromosomes 2, 5, 6, 7, 11, 13, 16, and 20 (53). More recent genomic searches have shown a close association of AR involving chromosomes 2, 3, 4, and 9 (Table 26.1) (54–60).

Risk factors for SAR include male sex, atopic parents with SAR, first-born child, early sensitization to food, and atopic dermatitis (61). A family history is a major risk factor for AR. In a study by Tang et al. (62), the development of atopic disease in the absence of parental family history was only present in 17%, whereas the risk increased to 29% when one parent or sibling was atopic. When both parents were atopic, the risk for developing an atopic disorder was 47% in the next generation. Studies have also shown that single nucleotide polymorphisms (SNPs), variations in DNA sequence seen in over 1% of the population that result from a single base change, have also been implicated in the pathogenesis of AR. Genome-wide association studies use reduced sets of SNPs to allow genotyping across the genome. These SNPs are then associated with the phenotype in AR in either a family-based or a case–control study design (63). Many of these SNP studies have been carried out in Asian populations,

especially in Korea and Japan. SNPs have been reported in molecules, including chemokines and their receptors; interleukins and their receptors; angiotensin-converting enzyme inhibitor and angiotensinogen genes; and eosinophil peroxidase and leukotrienes (60). A number of studies have also investigated polymorphisms in different genes. Polymorphisms in the CD14 gene have been associated with the severity of AR (64). Different polymorphisms of ADAM33 have been correlated to Japanese cedar pollinosis (65). Additionally, polymorphisms and haplotypes of FOXJ1 and the FcgRIIa gene have been associated with AR (66,67). In European-pooled analyses, SNPs within the toll-like receptor 4 (TLR-4) and tumor-necrosis factor (TNF) genes may increase the risk of AR in children (61). Furthermore, a large European study identified chromosome 11 open reading frame 30 (C11orf30) as a genome-wide significant locus for AR. A meta-analysis of genome-wide association studies with cat, dust mite and pollen allergies among Europeans identified 16 shared susceptibility loci, of which eight have been previously associated with asthma (63).

TABLE 26.1 GENOMIC SEARCHES CONDUCTED IN ALLERGIC RHINITIS

POPULATION	SAMPLE	ASSOCIATED CHROMOSOMAL REGIONS
Danish	424 individuals from 100 families, of which selection was made of 33 families with at least two siblings diagnosed with AR	Principal association: 4q24-q27. Other candidate regions: 2q12-q33, 3q13, 4p15-q12, 5q13-q15, 6p24-p23, 12p13, 22q13, y Xp21
Japanese	48 Japanese families (188 members) with at least two siblings with AR due to *Dactilys glomerata*	1p36.2, 4q13.3 y 9q34.3 Weak linkage to 5q33.1
Danish	424 individuals from 100 families	Region 4q32.2
French	295 families with at least one asthmatic	2q32, 3p24-p14, 9p22 and 9q22-q34 with RA 1p31 p with asthma and AR
Swedish	250 families initially included in an atopic dermatitis linkage study	Most intense association: 3q13, 4q34-35 y 18q12

		Weakest association: 6p22-24, 9p11-q12, 9q33.2-34.3 y 17q11.2
Danish	Three independent populations with a total of 236 families, including 125 sibling couples with rhinitis	3q13.31

AR, allergic rhinitis.

Adapted from Dávila I, Mullol J, Ferrer M, et al. Genetic aspects of allergic rhinitis. *J Investig Allergol Clin Immunol*. 2009;19(1):25–31.

Genetics alone cannot explain the increasing prevalence of AR, and this highlights the importance of environmental factors and epigenetic mechanisms in the pathology of AR (68). Epigenetics is the study of potentially heritable changes in gene expression that does not involve changes to the underlying DNA sequence. It may involve processes such as histone acetylation or DNA methylation which alters mRNA expression, modifies chromatin structure, and may either facilitate or prevent binding of transcription factors to promoter regions. DNA methylation may be a useful biomarker for phenotyping of AR and has useful diagnostic potential because it is more stable and easier to measure than mRNA and proteins (68). One study suggests the beneficial effects of allergen immunotherapy may be because of reduced DNA methylation of the FoxP3 promoter region in regulatory T cells. Additionally, several mouse model studies of SAR demonstrated DNA methylation changes expressed in CD4^{+} T cells (69).

Gene–environment interaction may also play a role in the epidemic rise of allergic diseases. One theory that has garnered much worldwide attention using gene expression measurements is the *hygiene hypothesis* which states that environmental exposures to high levels of microbial components, such as seen in traditional farms, may prevent sensitization to inhalant allergens and development of allergic diseases by upregulating expression of TLRs as well as regulatory cytokines, such as interleukin 10 (IL-10) and transforming growth factor β (70,71). Additionally, there is evidence that protection of AR from farm exposures could be effective during pregnancy. Pregnant women exposed to farm stables have an increased expression of receptors involved in innate immunity, including TLR-2, TLR-4, and CD14 (72).

ETIOLOGY

Pollen and mold spores are the allergens responsible for intermittent AR or SAR; Chapters 6 and 7 discuss the importance of these seasonal allergens in detail. Occasionally, PAR may be the result of exposure to an occupational allergen. Symptoms tend to be perennial but not constant because there is a clear, temporal association with workplace exposure. Some causes of occupational rhinitis include laboratory animals (rats, mice, guinea pigs, etc.), grains (bakers and agricultural workers), medications such as *psyllium* or *penicillium,* wood dust, particularly hard woods (mahogany, Western red cedar, etc.), latex, and chemicals (acid anhydrides, platinum salts, glues, and solvents) (73). Occupational immunologic diseases, including rhinitis, are discussed in detail in Chapter 25.

Although some clinicians believe that food allergens may be significant factors in the cause of persistent AR, a direct immunologic relationship between ingested foods and persistent rhinitis symptoms has been difficult to establish. Rarely, hypersensitivity to dietary proteins may induce the symptoms of non-SAR. Double-blind food challenges almost never confirm such reactions (74). Cow's milk is often the food suspected of precipitating or aggravating upper respiratory symptoms. Usually, however, the overwhelming majority of patients with proven food allergies do not have isolated nasal symptoms; instead, they exhibit other symptoms, including gastrointestinal disturbances, urticaria, angioedema, asthma, and anaphylaxis, in addition to rhinitis, after ingestion of the specific food.

Cross-reactive allergens between food and inhalant allergens are common. Patients with AR owing to birch and, to a lesser extent, other *Betulaceae* (hazel, alder) pollen frequently develop oral allergic symptoms to tree nuts, fruits, and vegetables, including apples, carrots, celery, and potatoes (75). Most patients develop mild symptoms, but anaphylaxis may occur very rarely from these cross-reacting foods. Some birch or hazel pollen allergens cross-react with those of fresh apples, especially those located just beneath the skin. Baked apples are tolerated as apple sauce (76). Ragweed-sensitive individuals may experience symptoms when eating banana or melon. Latex-sensitive individuals may develop symptoms when ingesting avocado, banana, chestnut, kiwi fruit, or other foods (77). Nonspecific irritants and infections may influence the course of persistent (perennial) AR. Children with this condition appear to have a higher incidence of respiratory infections that tend to aggravate the condition and may lead to the development of complications. Irritants such as pool chlorine, glues, hairsprays, laundry detergent, perfumes, tobacco smoke, and air pollutants (sulfur dioxide, volatile organic compounds, particulate matter, ozone, diesel

exhaust particles, and nitrogen dioxide) can aggravate the symptoms (78). Cold drafts, chilling, and sudden changes in ambient temperature are also implicated in symptom exacerbation, and these features indicate that the patient has concurrent nonallergic rhinitis (NAR).

CLINICAL FEATURES

The major symptoms of AR are sneezing, rhinorrhea, nasal pruritus, and nasal congestion, although patients may not have the entire symptom complex. When taking a history, one should record the specific characteristics of the symptoms, as follows:

- Define the onset and duration of symptoms and emphasize any relationship to seasons or life events, such as changing residence or occupation, or acquiring a new pet.

- Define the current symptoms, including secretions, degree of congestion, sneezing, and nasal itching, or sinus pressure and pain. Obtain a history regarding ocular symptoms, such as itching, lacrimation, puffiness, and chemosis; pharyngeal symptoms of a mild sore throat, throat clearing, and itching of the palate and throat; and associated systemic symptoms of malaise, fatigue, or sleep disturbances.

- Identify exacerbating factors, such as seasonal or perennial allergens and nonspecific irritants (e.g., cigarette smoke, illicit drug use, chemical fumes, cold air, etc.).

- Identify other associated allergic diseases, such as asthma or atopic dermatitis, or a family history of allergic diathesis.

- Obtain a complete medication history, including both prescription and over-the-counter medications.

Drug history is important because several medications can provoke or exacerbate rhinitis symptoms. These include antihypertensive medications, aspirin, or other nonsteroidal anti-inflammatory drugs (NSAIDs) oral contraceptives, and in particular, topical sympathomimetics/nasal decongestants which can provoke *rhinitis medicamentosa* (RM) if used for extended periods of time without the use of intranasal corticosteroids (79,80).

Obtain a careful occupational history. The occupational history may be relevant either as a direct cause of AR or because of workplace triggers that exacerbate preexisting rhinitis (81). It is important to recognize occupational rhinitis because it usually precedes the development of occupational asthma, and

therefore, these patients should be more closely monitored to prevent the development of occupational asthma. Professions most at risk for occupational asthma include bakers, furriers, and animal laboratory workers (82).

Identify patients with pollen-food syndrome or oral allergy syndrome. Patients with AR can develop oral symptoms to raw fruits and vegetables. It is characterized by an immediate, IgE reaction induced by prior sensitization to pollen rather than primary sensitization to a food allergen. Cross-reactivity depends on specific epitopes shared by food allergens and pollen (83).

Sneezing is the most characteristic symptom, and occasionally, one may have paroxysms of 10 to 20 sneezes in rapid succession. Sneezing episodes may arise without warning, or they may be preceded by an uncomfortable itching or irritated feeling in the nose. Sneezing attacks result in tearing of the eyes because of activation of the nasal-lacrimal reflex. During the pollen season, nonspecific factors, such as particulate exposure, sudden drafts, air pollutants, or noxious irritants, may also trigger violent sneezing episodes. The rhinorrhea is typically a thin discharge, which may be quite profuse and continuous. Because of the copious nature of the rhinorrhea, the skin covering the external nose and the upper lip may become irritated and tender. Purulent discharge is never seen in uncomplicated AR, and its presence usually indicates secondary infection. Nasal congestion resulting from swollen turbinates is a frequent complaint. Early in the season, the nasal obstruction may be more troublesome in the evening and at night, only to become almost continuous as the season progresses. If the nasal obstruction is severe, interference with aeration and drainage of the paranasal sinuses or the eustachian tube may occur, resulting in complaints of headache or earache. The headache is of the so-called *vacuum type*, presumably caused by the development of negative pressure when air is absorbed from the obstructive sinus or middle ear. Patients also complain that their hearing is decreased and that sounds seem muffled. Patients may also notice a crackling sensation in the ears, especially when swallowing. Nasal congestion alone, particularly in children, occasionally may be the major or sole complaint. With continuous severe nasal congestion, the senses of smell and taste may be lost. Itching of the nose may also be a prominent feature, inducing frequent rubbing of the nose, particularly in children. Eye symptoms (pruritus, erythema, and lacrimation) often accompany the nasal symptoms. Patients with severe eye symptoms often complain of photophobia, inability to wear contact lenses, and sore, tired eyes. Conjunctival injection and chemosis often occur. There is marked itching of the ears, palate, throat, or face, which may be extremely annoying. Because of irritating sensations in the throat and the posterior drainage of the nasal

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secretions, a hacking, nonproductive cough may be present. Lower respiratory tract symptoms, including cough, wheeze, and exertional dyspnea, may be associated with AR even in the absence of overt asthma. Bronchial hyperreactivity can be induced by changes in histamine/methacholine bronchial provocation doses after seasonal allergy exposure in atopic patients (84). Disorders of the upper and lower respiratory tract often coexist; most asthmatics have rhinitis or rhinosinusitis (85), whereas a significant minority of individuals with AR have coexistent asthma (86). Rhinitis/rhinosinusitis may impair asthma control and should always be considered in the assessment of patients with poorly controlled asthma (87).

Some patients have systemic symptoms of SAR. Complaints may include weakness, malaise, irritability, fatigue, and anorexia. Certain patients relate that nausea, abdominal discomfort, and poor appetite appear to occur with swallowing excess mucous.

A characteristic feature of the symptom complex is the periodicity of its appearance. Symptoms usually recur each year for many years in relation to the duration of the pollinating season of the causative plant. The most sensitive patients exhibit symptoms early in the season, almost as soon as the pollen appears in the air. The intensity of the symptoms tends to follow the course of pollination, becoming more severe when the pollen concentration is highest and waning as the season ends, when the amount of pollen in the air decreases. In some patients, symptoms disappear suddenly when the pollination season is over, whereas in others, symptoms may disappear gradually over a period of 2 to 3 weeks after the pollination season is completed. There may be an increased reactivity of the nasal mucosa after repeated exposure to the pollen. This local and nonspecific increased reactivity has been termed the *priming effect* (88). Under experimental conditions, a patient may respond to an allergen, not otherwise considered clinically significant if they were not exposed or primed to a clinically significant allergen. The nonspecificity of this effect may account for the presence of symptoms in some patients beyond the termination of the pollinating season because an allergen not clinically important by itself may induce symptoms in the *primed* nose. For example, a patient with positive skin tests to mold antigens and ragweed and no symptoms until August may have symptoms until late October, after the ragweed-pollinating season is over. The symptoms persist because of the presence of molds in the air, which affect the primed mucous membrane. In most patients, however, this does not appear to occur (89). The presence of a secondary infection or the effects of nonspecific irritants on inflamed nasal membranes may also prolong and influence the

degree of rhinitis symptoms beyond the specific pollinating season. Some nonspecific irritants include tobacco smoke, paints, newspaper ink, and laundry soap/detergent. Rapid atmospheric changes may aggravate symptoms in predisposed patients. Nonspecific air pollutants may also potentiate the symptoms of AR, such as sulfur dioxide, ozone, carbon monoxide, and nitrogen dioxide.

These symptoms of AR may exhibit periodicity within the season. Many patients tend to have more intense symptoms in the morning because most windborne pollen is released in greatest numbers between sunrise and 9:00 AM. Some specific factors such as rain may decrease symptoms of rhinitis because rain can clear pollen from the air. Also, dry windy days may increase symptoms because higher concentrations of pollen may be distributed over larger areas. The symptoms of PAR are similar to seasonal rhinitis. The decreased severity of symptoms seen in some patients may lead them to interpret their symptoms as resulting from *sinus trouble* or *frequent colds*. Nasal congestion may be the dominant symptom, particularly in children, in whom the passageways are relatively small. Sneezing, clear rhinorrhea, and itching of the eyes, ear, nose, and throat accompanied by lacrimation may also occur. The presence of itching in the nasopharyngeal and ocular areas is consistent with an allergic cause of the chronic rhinitis. The chronic nasal obstruction may cause mouth breathing, snoring, almost constant sniffing, and a nasal twang to the voice. The obstruction may worsen or be responsible for the development of obstructive sleep apnea. Because of the constant mouth breathing, patients may complain of a dry, irritated, or sore throat. Anosmia may occur in patients with marked chronic nasal obstruction. Protracted sneezing episodes on awakening or in the early morning hours are a complaint. Because the chronic edema involves the opening of the eustachian tube and the paranasal sinuses, dull frontal headaches and ear symptoms, such as decreased hearing, fullness, and popping of the ears are common. In children, there may be recurrent episodes of serous otitis media. Chronic nasal obstruction may lead to eustachian tube dysfunction. Persistent, low-grade nasal pruritus leads to almost constant rubbing of the nose and nasal twitching. In children, recurrent epistaxis may occur because of the friability of the mucous membranes, sneezing episodes, forceful nose blowing, or nose picking. After exposure to significant levels of an allergen, such as close contact with a pet or when dusting the house, the symptoms may be as severe as in the acute stages of SAR. Constant, excessive postnasal drainage of secretions may be associated with a chronic cough or a continual clearing of the throat.

Physical Examination

Most abnormal physical findings are present during the acute stages of disease, whether patients are having PAR or SAR. The physical findings commonly recognized include:

- Nasal obstruction and associated mouth breathing.

- Pale to bluish nasal mucosa and enlarged (boggy) inferior turbinates.

- Clear nasal secretions (whitish secretions may be seen in patients experiencing severe AR).

- Clear or white secretions along the posterior wall of the nasopharynx.

- Conjunctival erythema, lacrimation, and puffiness of the eyes.

The physical findings, which are usually confined to the nose, ears, and eyes, aid in the diagnosis. Rubbing of the nose and mouth breathing are common findings. Some children will rub the nose in an upward and outward direction, which has been termed the *allergic salute*. The eyes may exhibit excessive lacrimation. The sclera and conjunctivae may be reddened, and chemosis is often present. The conjunctivae may be swollen and may appear granular, and the eyelids are often swollen. The skin above the nose may be reddened and irritated because of the continuous rubbing and blowing. Examination of the nasal cavity discloses a pale, wet, edematous mucosa, frequently bluish in color. A clear, thin nasal secretion may be seen within the nasal cavity. Swollen turbinates may completely occlude the nasal passageway and severely affect the patient. Occasionally, there is fluid in the middle ear, resulting in decreased hearing. The pharynx may have streaks of lymphoid tissue, sometimes called "cobblestoning" because of the appearance. The nose and eye examination is normal during asymptomatic intervals in those with SAR.

In patients with PAR, the physical examination may aid in the diagnosis, particularly in a child, who may constantly rub his nose or eyes. These include a gaping appearance because of the constant mouth breathing, and a broadening of the midsection of the nose. There may be a transverse nasal crease across the lower third of the nose where the soft cartilaginous portion meets the rigid bony bridge. This is the result of the continual rubbing and pushing of the nose to relieve itching. The mucous membranes are pale, moist, and boggy, and may have a bluish tinge. The nasal secretions are usually clear and watery, but may be more mucoid and microscopically may show large numbers of eosinophils. Dark circles under the eyes, known as *allergic shiners,* appear in some children. These

are presumed to be due to venous stasis secondary to constant nasal congestion. The conjunctiva may be injected or may appear granular. In children affected with PAR early in life, narrowing of the arch of the palate may occur. These children may develop facial deformities, such as dental malocclusion or gingival hypertrophy. The throat is usually normal on examination, although the posterior pharyngeal wall may exhibit prominent lymphoid follicles.

PATHOPHYSIOLOGY

The nose has the following six major functions: an olfactory organ, a resonator for phonation, a passageway for airflow in and out of the lungs, a means of humidifying and warming inspired air, a filter of noxious particles from inspired air, and a part of the immunologic responses of the nose and sinuses (90,91). Allergic reactions in the nasal mucous membranes may markedly affect the nose's major functions. AR is an IgE-mediated disease characterized by an eosinophilic inflammatory response with manifestations of nasal congestion, rhinitis, pruritus, and sneezing in response to inhaled allergens in a previously sensitized subject (92–94). Symptoms normally involve an *early phase* that clears within 1 to 2 hours, followed by a *late phase* that may last up to 12 to 24 hours (95).

IgE antibodies bind to high-affinity receptors (FcεRI) on mast cells and basophils and to low-affinity receptors (FcεRII or CD23) on other cells, such as monocytes, eosinophils, B cells, and platelets (91). Upon exposure of the allergen into the respiratory tract, the allergen is first internalized by antigen-presenting cells (APCs), which include macrophages, $CD1^+$ dendritic cells, B lymphocytes, and epithelial cells (96). After the allergen is taken up by the APC, it is then processed to a small peptide that binds to specific major histocompatibility complex (MHC) class II molecules via $CD4^+$ T lymphocytes (97). Nasal allergen provocation has been associated with increased HLA-DR and HLA-DQ (these are αβ heterodimers of class II MHC molecules that function as cell surface receptor proteins on antigen presenting cells) positive cells in the lamina propria and epithelium in allergic subjects (98). The MHC class II–peptide complex is then expressed on the cell surface where it is recognized by the T_H0 receptor and other co-stimulatory molecules, resulting in differentiation into T_H2 $CD4^+$ lymphocytes that produce cytokines like IL-4, IL-5, and IL-13. This is the crucial early event in allergic sensitization and the key to the development of allergic inflammation via T_H2 induction. Anergy of the T_H2 differentiation pathway may occur if there is a lack of a second cell-to-cell

contact between CD80 or CD86 on APCs and CD28 on T cells (99).

After IgE antibodies specific for a certain allergen are synthesized and secreted, they bind to high-affinity FcεRI IgE receptors on the surface of mast cells. Mast cells are abundant in the epithelial compartment of the nasal mucosa in AR subjects and may be easily activated upon re-exposure to the allergen. On nasal re-exposure to allergen, the allergen cross-links the specific cell-bound IgE antibodies on the mast cell surface in a calcium-dependent process, resulting in mast cell degranulation and release of a number of preformed and newly synthesized mediators of inflammation. These mediators include histamine, leukotrienes, prostaglandins, proteases, proteoglycans, platelet-activating factor, bradykinin, cytokines, and chemokines (91). These mediators are responsible for mast cell–mediated allergic reactions, resulting in immediate-type rhinitis symptoms, including edema, increased vascular permeability, and nasal discharge. Histamine, the major mediator of AR, stimulates the secretion of mucus and nasal discharge, as well as the sensory nerve endings of the trigeminal nerve to induce sneezing and pruritus. Histamine, leukotrienes, and prostaglandins may also act on blood vessels and cause nasal congestion (91).

The normal nasal submucosa contains approximately $7,000/mm^3$ mast cells, but only $50/mm^3$ mast cells are in the nasal epithelium (91). However, the superficial nasal epithelium contains 50-fold more mast cells and basophils in AR compared to NAR subjects (100). Nasal mast cells are predominantly connective tissue mast cells located in the nasal lamina propria, although 15% are epithelial mucosal mast cells. Mucosal mast cells express tryptase without chymase and may proliferate in AR under the influence of T_H2 cytokines.

Mast cells and their mediators are important components of the early-phase response given mast cell degranulation in the nasal mucosa and detection of histamine, leukotriene C_4 (LTC_4) and prostaglandin D_2 (PGD_2) in nasal washings (91). Additionally, the early-phase response may also be associated with an increase in neuropeptides such as calcitonin gene-related peptide (cGRP), substance P, vasoactive intestinal peptide (VIP) and increasing numbers of cytokines, including IL-1, IL-3, IL-4, IL-5, IL-6, granulocyte macrophage colony-stimulating factor (GM-CSF), and TNF-α (101–105). These mast cell–derived cytokines promote further IgE production and mast cell and eosinophil growth, survival, and chemotaxis. IL-1, IL-5, and TNF-α promote eosinophil movement by increasing the expression of endothelial adhesion molecules. Eosinophils may secrete a plethora of cytokines, including IL-3, IL-4, IL-5, IL-10, and GM-CSF, resulting in mast cell growth and T_H2 proliferation.

Eosinophils may also act in an autocrine manner and produce IL-3, IL-5, and GM-CSF that are important in hematopoiesis, differentiation, and survival of eosinophils (91). There is an accumulation of CD4$^+$ lymphocytes, eosinophils, neutrophils, and basophils during an allergic inflammatory process (106). Eosinophils release oxygen-free radicals and proteins, including eosinophil major basic protein, eosinophil cationic protein (ECP), and eosinophil peroxidases, which may disrupt the respiratory epithelium and promote further mast cell mediator release and hyperresponsiveness (107,108). Eosinophils also increase during seasonal exposure, and the number of eosinophil progenitors in the nasal scrapings increases after exposure to allergens, thus correlating with the severity of seasonal disease.

Almost 4 to 6 hours after allergen stimulation, the early-phase may be followed by the late-phase response which may last anywhere from 18 to 24 hours. The late-phase response is characterized by a prolongation of sneezing, rhinorrhea, and a sustained nasal congestion. The late-phase response may also trigger a systemic inflammation that may augment inflammation in the upper and lower airways, suggesting a link to asthma. The late-phase response is characterized by infiltration of T lymphocytes, basophils, eosinophils, and neutrophils in the nasal submucosa. In those who undergo nasal challenge, the late-phase reaction occurs in greater than 50% of AR subjects (91). Unlike the early-phase response, PGD_2 and tryptase are not detected in the late-phase response. The absence of these mediators during the late-phase response is consistent with basophil-derived histamine release rather than mast cell involvement. Basophils are significantly increased in nasal lavage fluid 3 to 11 hours after allergen challenge, suggesting their role in late-phase reactions (109).

LABORATORY FINDINGS

The diagnosis of AR is based on both clinical history and diagnostic studies. *In vitro* allergen-specific IgE (sIgE) testing is advantageous in a number of clinical settings where skin-prick testing cannot be performed, such as urticaria with dermatographism, severe eczema/allergic contact dermatitis (making interpretation challenging), or use of medications, such as histamine-1/histamine-2 antagonists, tricyclic antidepressants, or β-blockers. It may also be advantageous to perform *in vitro* testing in infants and young children. There is no risk of anaphylaxis with *in vitro* testing. Conversely, *in vitro* testing offers a lower sensitivity as compared to skin-prick testing at a higher cost, and the results are not readily available to both the clinician and the patient.

In chronic rhinitis, the presence of large numbers of eosinophils suggests an allergic cause, although NAR with eosinophilia syndrome (NARES) certainly occurs. The absence of nasal eosinophilia does not exclude an allergic cause, especially if the test is performed during a relatively quiescent period of the disease, or in the presence of bacterial infection when large numbers of polymorphonuclear neutrophils obscure the eosinophils. Peripheral blood eosinophilia of (absolute eosinophil count > 500/µL) may or may not be present in active SAR. A significantly elevated concentration of serum IgE may occur in some patients with AR, but many other conditions (including racial factors) may increase the serum levels of total IgE, such as concomitant atopic dermatitis. Thus, the measurement of total serum IgE is barely predictive for allergy screening in rhinitis and should not be used as a diagnostic tool (1).

DIAGNOSIS

The diagnosis of SAR (intermittent) usually presents no difficulty by the time the patient has had symptoms severe enough to seek medical attention. The seasonal nature of the condition, the characteristic symptom complex, and the physical findings should establish a diagnosis in almost all cases. If the patient is first seen during the initial or second season, or if the major symptom is conjunctivitis, there may be a delay in making the diagnosis from the history alone. Additional supporting evidence is a positive history of allergic disorders in the immediate family and a collateral history of other allergic disorders in the patient. After the history is taken and the physical examination is performed, skin tests should be performed to determine the reactivity of the patient against the suspected allergens. For the proper interpretation of a positive skin test, it is important to remember that patients with AR may exhibit positive skin tests to allergens other than those that are clinically important. In SAR, it has been demonstrated that prick testing with standardized extracts is adequate for diagnostic purposes in many patients if standardized extracts are used. Intradermal testing when positive may not always correlate with allergic disease (110,111). Skin testing should be performed and interpreted by trained personnel because results may be altered by the distance placed between allergens (112), the application site (back versus arm), the type of device used for testing (113), the season of the year tested (114), and the quality of extracts used for testing (115).

The first immunoassay used to accurately measure serum sIgE was the radioallergosorbent test (RAST) (116–118). Newer immunoassays use enzyme-labeled anti-IgE; they have been employed as a diagnostic aid in some allergic

diseases. Immunoassays of circulating sIgE can be used instead of skin testing when high-quality extracts are not available, when a control skin test with a diluent is consistently positive, when antihistamine therapy cannot be discontinued, or widespread skin disease is present. Initially, RAST, then enzyme-based anti-IgE assays appear to correlate fairly well with other measures of sensitivity, such as skin tests, endpoint titration, histamine release, and provocation tests. The frequency of positive reactions obtained by skin testing is usually greater than that found with serum or nasal RAST or enzyme assay. In view of these findings, the serum assays may be used as a supplement to skin testing. Skin testing is the diagnostic method of choice to demonstrate IgE antibodies. When the skin test is positive, there is little need for other tests. When the skin test is dubiously positive, the *in vitro* diagnostic test will, as a rule, be negative. Therefore, the information obtained by measuring serum sIgE usually adds little to that gleaned from critical evaluation of skin testing with high-quality extracts.

DIFFERENTIAL DIAGNOSIS

The diagnosis of AR must be established carefully because an incorrect diagnosis could result in expensive treatments and major alterations in a patient's lifestyle and environment. Several medical conditions may be confused with persistent AR (Table 26.2). The main causes of persistent nasal congestion and discharge include RM, drugs, pregnancy, nasal foreign bodies, other bony abnormalities of the lateral nasal wall, concha bullosa (air cell within the middle turbinate), enlarged adenoids, nasal polyps, cerebrospinal fluid (CSF) rhinorrhea, tumors, hypothyroidism, ciliary dyskinesia from cystic fibrosis, primary ciliary dyskinesia, Kartagener syndrome, granulomatous diseases (e.g., sarcoidosis, granulomatosis with polyangiitis, midline granuloma), nasal mastocytosis, congenital syphilis, gustatory rhinitis, gastroesophageal reflux, atrophic rhinitis, eosinophilic granulomatosis with polyangiitis (formerly known as Churg–Strauss vasculitis), allergic fungal sinusitis, and NARES.

Rhinitis Medicamentosa

A condition that may enter into the differential diagnosis is RM or rebound nasal congestion. RM is a drug-induced, nonallergic form of rhinitis in which the nasal mucosa is induced or aggravated by the excessive or improper use of nasal decongestants (119). The pathophysiology of RM is not well understood and is thought to be a dysregulation of sympathetic/parasympathetic tone, resulting in increased parasympathetic activity, vascular permeability, and edema formation

by altering vasomotor tone, thus creating the rebound congestion (120). Sympathomimetic amines, such as pseudoephedrine, phenylephrine, and ephedrine, activate sympathetic nerves through release of endogenous norepinephrine causing vasoconstriction (121). Imidazolines (e.g., xylometazoline, oxymetazoline, clonidine) cause vasoconstriction primarily through α2-adrenoreceptors (122). In patients with RM, discontinuation of the offending agent along with a course of oral corticosteroids is recommended.

TABLE 26.2 DIFFERENTIAL DIAGNOSIS OF NONALLERGIC RHITINIS

Associated drugs
- Topical α-adrenergic agonists
- Oral estrogens
- Ophthalmic and oral β-blockers

Infections
- Chronic sinusitis
- Tuberculosis
- Syphilis
- Fungal infection

Systemic conditions
- Cystic fibrosis
- Immunodeficiencies
- Immotile cilia syndrome
- Hypothyroidism
- Rhinitis of pregnancy

Structural abnormalities
- Marked septal deviation
- Concha bullosa
- Nasal polyps
- Adenoidal hypertrophy
- Foreign body

Neoplasms

- Squamous cell carcinoma
- Nasopharyngeal carcinoma

Granulomatous diseases

- Granulomatosis with polyangiitis (GPA; formerly Wegener granulomatosis)
- Sarcoidosis
- Midline granuloma
- Eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg–Strauss vasculitis)

Other

- Atrophic rhinitis
- Gustatory rhinitis
- Allergic fungal sinusitis
- Gastroesophageal reflux disease
- Nonallergic rhinitis with eosinophilia syndrome (NARES)

Drugs

A number of different drugs may cause nasal congestion. Examples include antihypertensive medications such as reserpine, hydralazine, guanethidine, methyldopa, prazosin, doxazosin, reserpine, and chlorothiazide; β-adrenergic blockers such as nadolol and propranolol; phosphodiesterase-5 inhibitors such as sildenafil, vardenafil, tadalafil, oral contraceptives and exogenous hormones; antidepressants/antipsychotics; cocaine; and NSAIDs. Discontinuation of these drugs for a few days results in marked symptomatic improvement.

Cyclic changes in rhinitis intensity may be related to the changes in relative concentrations of the complex mix of hormones during the menstrual cycle. In nasal provocation experiments, allergic patients on oral contraceptives having grass challenges had less nasal congestion at day 14 of the menstrual cycle and more sneezing at the end of the cycle (123). Thus, oral contraceptives affect nasal reactivity in complex ways and usually can be continued in patients with AR.

Cocaine sniffing is often associated with congestion, rhinorrhea, diminished

olfaction, and septal perforation (124). Aspirin and other NSAIDs commonly induce rhinitis. In a population-based random sample, aspirin intolerance was more frequent in subjects with AR than those without AR (125). In about 10% of adult patients with asthma, aspirin and other NSAIDs that inhibit cyclooxygenase (COX) enzymes precipitate asthmatic attacks and nasal reactions (126). This distinct clinical syndrome, called aspirin-exacerbated respiratory disease (AERD), is characterized by an atypical sequence of symptoms, intense eosinophilic inflammation of the nasal and bronchial tissues, combined with an overproduction of cysteinyl leukotrienes. After ingestion of aspirin or other NSAIDs, an acute asthma attack occurs within 3 hours, usually accompanied by profuse rhinorrhea, conjunctival injection, periorbital edema, and sometimes a scarlet flushing of the head and neck. The inflammatory cell populations in the nasal mucosa of aspirin-sensitive rhinitis patients have been studied. In comparison to normal subjects, there is an increase in eosinophils, mast cells, and activated T cells. Marked increases in the numbers of IL-5 mRNA$^+$ cells and lower numbers of IL-4 mRNA$^+$ cells are observed in aspirin-sensitive patients. No differences are recognized for either IL-2 or IFN-γ. The predominance of macrophages, and the disproportionate increase in IL-5 compared to IL-4 mRNA expression suggest that factors other than allergic mechanisms may be important in this disease (105,127). A similar increase in IL-5, an overexpression of LTC$_4$ synthetase, and increase in cysteinyl leukotriene 1 receptor numbers have been noted in the bronchi or cells of patients with AERD (127,128).

Pregnancy

Rhinitis of pregnancy has been attributed to increasing concentrations of female hormones during pregnancy, and the need for swollen mucosae with mucous hypersecretion for protection of the vagina and cervix (129). It is estimated to impact up to 10% to 30% of pregnant women and is limited to the gestational period (130). The rhinitis characteristically begins at the end of the first trimester and then disappears immediately after delivery (131). It has been reported that increased nasal congestion occurs in 22% to 72% of gravidas with asthma (132). The course of rhinitis of pregnancy is variable, and although many patients remain unchanged, approximately one-third may actually have a worsening of their condition during pregnancy similar to the pattern of asthma in pregnancy (133).

Foreign Body

On rare occasions, a patient with a foreign body in the nose may be thought to have chronic rhinitis. Foreign bodies usually present as unilateral nasal obstruction accompanied by a foul, purulent nasal discharge. Children may place foreign bodies into the nose, most commonly peas, beans, buttons, and erasers. Nasal foreign bodies resulting in chronic rhinitis, however, are rarely seen in adults and are usually the result of trauma or comorbid mental illness (134). Sinusitis is often misdiagnosed if the nose is not examined properly. Examination is best done after secretions are removed so that the foreign body may be visualized. Common symptoms of nasal foreign body include nasal discharge, congestion, pain, and/or malodorous, mucopurulent discharge (135).

Physical Obstruction

Careful physical examination of the nasal cavity should be performed to exclude septal deviation, enlarged adenoids, choanal atresia, concha bullosa, and nasal polyps as a cause of nasal congestion.

Cerebrospinal Fluid Rhinorrhea

CSF rhinorrhea may rarely mimic AR (136). The majority of CSF rhinorrhea cases are the result of trauma (137). Cases of spontaneous (nontraumatic) CSF rhinorrhea may be a high or normal pressure leak, and can persist for months to years. There are reports of meningitis in 19% of patients with persistent CSF leak (138). The CSF is clear and watery in appearance, and may be either unilateral or bilateral (139). Obtaining β-2 transferrin levels from the nasal discharge establishes the diagnosis. The β-2 transferrin is only present in the CSF, perilymph, and aqueous humor. When present in nasal discharge, it is highly specific for CSF rhinorrhea (140). After localization of the leak with magnetic resonance or computed tomography (CT) cisternography or high-resolution CT examination, surgical repair is required to prevent meningitis (140).

Tumor

Several neoplasms may occur in the nasopharyngeal area. The most important are encephalocele, inverted papilloma, squamous cell carcinoma, sarcoma, and angiofibroma. Encephaloceles are generally unilateral. They usually occur high in the nose and occasionally within the nasopharynx. They increase in size with straining, lifting, or crying. Some have a pulsating quality. CSF rhinorrhea, or even meningitis, may develop as a complication of biopsy of these lesions.

Inverted papillomas have a somewhat papillary appearance. They are friable and more vascular than nasal polyps, and bleed more readily. They occur either unilaterally or bilaterally, and frequently involve the nasal septum as well as the lateral wall of the nose. A biopsy is necessary to confirm the diagnosis. Angiofibromas are the most common tumors in preadolescent boys (141). They arise in the posterior choana (choanae osseae) of the nasopharynx. They have a polypoid appearance but are usually reddish-blue in color. They do not pit on palpation. Angiofibromas are highly vascular tumors that bleed excessively when injured or when a biopsy is done. Larger tumors may invade bone and extend into adjacent structures (141). Carcinomas and sarcoma may simulate nasal polyps. They are generally unilateral, may occur at any site within the nasal chamber, are firm, and usually bleed with manipulation. As the disease progresses, adjacent structures become involved.

Hypothyroidism

In patients with hypothyroidism, an increase in thyroid-stimulating hormone results in edema of the nasal turbinates. Therefore, a careful review of systems and thyroid function studies are important to exclude hypothyroidism as a cause of nasal congestion.

Syphilis

In up to 70% of infants infected with syphilis, there is mucocutaneous involvement of the nasal passages causing rhinitis that is either present at birth or develops within first 3 months of life (142). *Saddle nose* deformity occurs secondary to ulceration of the nasal mucosa and cartilage.

Ciliary Disorders

With the dyskinetic cilia syndrome, patients may experience rhinitis symptoms secondary to abnormalities of mucociliary transport. The criteria for diagnosis include (a) absence or near absence of tracheobronchial or nasal mucociliary transport and (b) total or nearly total absence of dynein arms of the cilia in the nasal or bronchial mucosa. On electron microscopy, one may see defective radial spokes or transposition of a peripheral microtubular doublet to the center of the axoneme. The last criterion is (c) clinical manifestations of chronic upper and lower respiratory tract infections (i.e., sinusitis, bronchitis, and bronchiectasis) (143). Rare patients may have the triad of bronchiectasis, sinusitis, and *situs inversus* (Kartagener syndrome) (144). In some patients, cilia, although abnormal in structure, may be motile. The cilia in patients with this syndrome

can be distinguished from those in patients with asthma, sinusitis, chronic bronchitis, and emphysema, who may have nonspecific abnormalities in cilia structure.

Perennial Nonallergic Rhinitis

PAR comprises a heterogeneous group of at least seven subgroups. These include NARES, drug-induced rhinitis, gustatory rhinitis, hormone-induced rhinitis, atrophic rhinitis, rhinitis of the elderly, and idiopathic rhinitis. NARES is characterized by nasal eosinophilia, but there is currently no consensus on the degree of eosinophilia required because a range for 5% to 20% has been reported to be consistent with the condition (145,146). Because the pathophysiology of NARES is unknown, it has been equated to idiopathic rhinitis, local allergic rhinitis (LAR), a local inflammatory response induced by irritants, or as a precursor to AERD because NARES patients frequent have eosinophilic nasal polyps, bronchial hyperreactivity, and nonallergic asthma. NARES patients demonstrate perennial symptoms of sneezing, itching, rhinnorhea, nasal obstruction, and, occasionally, a loss of the sense of smell. The condition may occur in children and adults and usually has a favorable response to intranasal corticosteroids.

Idiopathic rhinitis, sometimes referred to as vasomotor or intrinsic rhinitis, is the most prevalent type of NAR. Its pathophysiology is unrelated to allergy or underlying systemic disease and usually not associated with nasal eosinophilia. In these patients, nasal symptoms, although similar to that of AR, are usually precipitated by nonspecific stimuli, such as smoke, perfume, strong odors, and barometric pressure changes. Although the pathophysiology of idiopathic rhinitis is unknown, some forms of idiopathic rhinitis may be disorders of the nonadrenergic, noncholinergic, or peptidergic neural system (147,148). Nasal peptidergic neurons (mainly sensory C fibers) are activated by those nonspecific stimuli, resulting in antidromic and orthodromic release of inflammatory neuropeptides which can exert side effects on the blood vasculature and mucous secreting glands and lead to the symptoms of idiopathic rhinitis (149). These fibers are thought to be primarily activated by the transient response potential (TRP) calcium ion channels whose ligands are demonstrated to be affected by temperature, mechanical, or osmotic stimuli, or as a spectrum of chemical irritants. The TRPV1 is activated by hot temperatures and has been shown to be a specific ligand for capsaicin. An acute exposure to capsaicin can activate TRPV1, whereas continuous exposure to capsaicin can desensitize this receptor (150). TRPA1 and TRPM8 channels may be stimulated by cold air (151) and

may be attenuated by capsaicin (152). Similar TRP pathways may play a significant role in gustatory rhinitis, (153) acute viral rhinosinusitis (154,155), rhinitis of the elderly, or even AR.

Atrophic Rhinitis

Primary atrophic rhinitis is a type of rhinitis that is more prevalent in lower socioeconomic populations in the developing world and characterized by progressive atrophy of the nasal mucosa and underlying bone, resulting in a nasal cavity that is widely patent but full of copious foul-smelling crusts (156). The infection may be attributed to *Klebsiella pneumoniae* sp. *ozaenae,* although its role as a primary pathogen is not fully documented. Symptoms usually consist of severe nasal congestion, hyposmia, and a constant smell. Decreased blood flow to the nasal mucosa contributes to the local atrophy and leads to the enlargement of the nasal space with paradoxic nasal congestion (157). Atrophic rhinitis can overlap in patients with NAR or AR. It must be distinguished from secondary atrophic rhinitis associated with radiation, trauma, excessive nasal surgery, and chronic granulomatous conditions.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) can be associated with rhinitis and recurrent otitis media, especially in children (158–160). The prevalence is thought to increase with age, and up to 22% of elderly individuals have GERD (161,162). A recent 10-year prospective cohort study found that those with nocturnal GERD were 60% more likely to develop rhinitis symptoms (163). Another recent study also found a link between GERD and rhinitis symptoms in patients even up to 75 years of age (164). The exact underlying mechanisms of the GERD–rhinitis association and whether treatment of GERD will improve rhinitis in different age groups merits further study.

Allergic Fungal Rhinosinusitis

The fungi responsible for allergic fungal rhinosinusitis (AFS) are predominantly of the Dematiaceae family (*Aspergillus* spp., *Rhizopus* spp., *Alternaria* spp., *Curvularia* spp., and *Bipolaris spicifera*) (165). AFS primarily occurs in atopic patients who develop an IgE-mediated response to the fungus, resulting in nasal polyps (166). The sinus mucosa shows a characteristic eosinophilic inflammation, with allergic mucin filling the sinuses. Elevated total IgE and fungal-specific IgG and IgE antibodies are commonly found (167). AFS is unilateral in more than 50% of patients but may involve several sinuses with

associated bone erosion. On CT scan, involved sinuses demonstrate the presence of an expandable lesion commonly with bone thinning and/or erosion, but bony invasion is not seen (168). The CT findings also included heterogeneous opacities, with areas of hyperattenuation (i.e., increased density on a CT scan, magnetic resonance imaging shows T2 hypointensity) (168). In areas where erosion/expansion has not occurred, the surrounding bone may appear thickened or osteitic from the chronic inflammation as compared to the uninvolved areas. Although often described as being *calcific*, the density of these opacities is actually a combination of the various metals (e.g., iron, magnesium, and manganese) concentrated by the fungal organisms, as well as the low-water and high-protein content of the mucin (168). One study reported that when used in combination with the presence of nasal polyps and Aspergillosis sIgE, the sensitivity and specificity of CT imaging is up to 70% and 100%, respectively (169). Treatment usually includes surgical intervention with polypectomy and marsupialization of the involved sinuses. Medical management involves long-term intranasal glucocorticosteroids with the use of systemic corticosteroids for more difficult cases (170). Several studies have reported that immunotherapy is helpful in AFS as adjunct treatment. These studies report better quality of life (170–173) with reduced corticosteroid requirements and need for repeat surgery. However, the studies have suffered from the absence of well-characterized controls, and doubt has been raised given the poor outcomes of fungal immunotherapy when used for other conditions, such as AR and asthma (174).

LOCAL ALLERGIC RHINITIS

LAR is a clinical entity characterized by symptoms suggestive of AR owing to a localized allergic response in the nasal mucosa in the absence of systemic atopy assessed by conventional diagnostic tests such as skin-prick test or determination of sIgE in serum (175). The prototypical LAR patient is a young female, nonsmoker with a family history of atopy and a history consistent with AR. Most LAR patients usually have moderate-to-severe symptoms that tend to worsen over time. Although LAR is more common in adults, 36% of subjects develop it in childhood (176–178).

More than 30% of subjects with LAR also report asthmatic symptoms (177–179). IgE may play an important role in nonatopic asthma, and may be produced locally as in the nasal mucosa of LAR patients (180). Several studies have demonstrated the local synthesis of IgE in the bronchial mucosa of atopic and nonatopic asthmatics, with increased expression of the IgE ε heavy chain germline and mature gene transcripts (ε chain mRNA) and local IgE class

switching (181,182).

The characterization of LAR has generated important clinical questions as to whether it develops into AR with systemic atopy or is a risk factor for asthma. The results of the first longitudinal study revealed that LAR has a low rate of conversion to AR that is similar to healthy controls (6.25% versus 5%) after 5 years of evaluation. This study periodically evaluated a cohort of 149 LAR patients and 130 control subjects using questionnaires, skin-prick tests, serum sIgE, lung function, and nasal allergen provocation test (177). LAR patients worsened over time, with impairment in quality of life, an increase in rhinitis persistence and severity, and new associations with conjunctivitis and asthma.

The diagnosis of LAR starts with the demonstration of an allergen-specific nasal response by means of nasal allergen provocation test and/or sIgE in nasal secretions or tissue (183). Nasal allergen provocation testing is considered the gold standard for LAR diagnosis. The nasal allergen provocation testing has a higher sensitivity than sIgE measurement in nasal secretions, because the measurement of sIgE in nasal secretions can vary depending on the technique used (184,185).

The treatment of LAR is similar to AR and includes education, allergen avoidance measures, pharmacologic treatment with intranasal corticosteroids, oral and intranasal antihistamines, and allergen immunotherapy (180,186).

COURSE AND COMPLICATIONS

The course of patients with AR is variable (187); one study reported 39% improved, 39% remained unchanged, and in 21%, the symptoms became worse (188). In another study, 8% of those with AR had remissions for at least 2 years' duration (187). In a study published in the 1970s, a chance for remission was better in those with SAR and if the disease was present for less than 5 years (189). The possibility of developing asthma as sequelae to AR may worry the patient(s). AR and positive allergy skin tests are significant risk factors for developing new asthma (190). A 10-year prognosis study for childhood AR found that asthma or wheezing developed in 19% of cases and was more common among those with PAR than those with SAR (191). Individuals with either of these diagnoses are about three times more likely to develop asthma than negative controls. However, upper and lower airway symptoms may develop simultaneously in about 25% of patients. Patients with AR may develop complications because of chronic nasal inflammation, including recurrent otitis media with hearing loss, impaired speech development, acute and chronic

sinusitis, recurrence of nasal polyps, abnormal craniofacial development, sleep apnea with its related complications (191,192), aggravation of asthma, and increased propensity to develop asthma. In patients with AR, a continuous allergen exposure results in persistent inflammation that upregulates expression of ICAM-1 and VCAM-1 in the inflamed epithelium (193). Because ICAM-1 is the ligand for almost 90% of rhinoviruses, its upregulation may be responsible for the increased prevalence of rhinovirus recovery in these patients. Poorly controlled symptoms of AR may contribute to sleep loss, secondary daytime fatigue, learning impairment, decreased overall cognitive functioning, decreased long-term productivity, and decreased quality of life. The symptoms of AR and skin test reactivity tend to wane with increasing age. In most patients, however, skin tests remain positive despite symptomatic improvement; therefore, symptomatic improvement does not necessarily correlate with skin test conversion to negative.

TREATMENT

There are three types of management of SAR or PAR: (a) avoidance therapy, (b) symptomatic therapy (pharmacologic treatment), and (c) immunotherapy. Aeroallergen avoidance and immunotherapy are reviewed in Chapter 13.

Overview of Pharmacologic Treatment

The current treatment strategy for AR consists of a stepwise approach based on symptom duration, severity, and associated comorbid conditions, such as conjunctivitis or asthma. Medical therapies are targeted at blocking symptoms from either the histamine-mediated early-phase response within the target tissue or the late-phase response. Pharmacotherapy in AR is generally divided into two broad classes—topical or oral agents. For the management of mild intermittent AR, the suggested initial pharmacologic therapy consists of an oral antihistamine, an intranasal antihistamine, or an oral decongestant. An oral nonsedating second-generation H_1-receptor antihistamine is recommended over a first-generation H_1-receptor antihistamine which is normally associated with more adverse effects, including sedation, impaired motor coordination, and excessive drying (194). When intermittent disease is moderate or severe, intranasal steroids provide an alternative to the aforementioned agents (91). For persistent moderate or severe AR, intranasal corticosteroids should be the first class of medications employed, with intranasal antihistamines as an alternative agent.

Investigation into the presence of allergic conjunctivitis should also take place because topical ocular H_1 antihistamines with mast cell stabilizing properties (i.e., cromolyn, nedocromil, olopatadine, azelastine, pemirolast) may be necessary to achieve better control of ocular symptoms in AR subjects who do not experience control of allergic conjunctival symptoms with the use of intranasal corticosteroids (195). Despite individual improvement seen in subjects with increased sneezing, pruritus, or conjunctival symptoms, clinical studies have demonstrated little benefit of adding oral antihistamines or a leukotriene-modifying agent like montelukast to an intranasal corticosteroid for treatment of moderate or severe AR (196). With all grades of severity, appropriate follow-up should occur in a reasonable period with therapy stepped down or intensified as tolerated. Specific drugs for the treatment of AR and other allergic diseases are covered in Chapters 33 to 38.

Intranasal Corticosteroids

Intranasal corticosteroids are the single most effective first-line therapy for moderate-to-severe AR. They are generally considered the most effective medications at managing the inflammatory component and relieving all four primary nasal symptoms of AR, including nasal congestion, rhinorrhea, pruritus, and sneezing. In addition, these agents may relieve oropharyngeal pruritus, cough associated with AR, itchy, watery eyes associated with allergic conjunctivitis, and improvement of asthma (197). The concept of delivering steroids intranasally was to minimize potential side effects of using systemic corticosteroids. In most studies, intranasal corticosteroids were shown to be more effective than the combined antihistamines and leukotriene antagonists in the treatment of SAR. Additionally, in most patients who are unresponsive or noncompliant with intranasal corticosteroids, other viable alternatives include using an antihistamine in combination with a leukotriene antagonist or a decongestant (198). The onset of therapeutic efficacy of intranasal corticosteroids normally occurs between 3 and 12 hours. Corticosteroids are lipid soluble and exert their effect by binding to the cytoplasmic glucocorticoid receptors before being translocated to the nucleus. After entering the cell nucleus, the activated corticosteroid receptor attaches as a dimer to specific sites on DNA in the promoter region of steroid-responsive genes to either induce or suppress gene transcription patterns and downregulate the inflammatory response (199). The mRNA transcripts induced during this process then undergo posttranscriptional processing and are transported to the cytoplasm for translation by ribosomes with reduced production of pro-inflammatory proteins

(91). After posttranslational processing, the new proteins are either released extracellularly or retained by the cell for intracellular activity. Additionally, the activated glucocorticoid receptors may interact directly with other transcription factors in the cytoplasm and alter the steroid responsiveness of the target cell (91).

Corticosteroids have specific effects on inflammatory cells and chemical mediators. Intranasal glucocorticoids inhibit the uptake and/or processing, but not the presentation of antigen by airway Langerhans cells that reduces the secondary inflammatory response and symptoms of AR (200,201). Intranasal corticosteroids reduce eosinophils and their products, resulting in decreased eosinophil survival. Corticosteroids may also reduce the influx of basophils and mast cells in the epithelial layers of the nasal mucosa (91). Corticosteroids inhibit T-cell activation and reduce the production of pro-inflammatory cytokines, including IL-2, IL-3, IL-4, IL-5, and IL-13 and their receptors, resulting in reduced vascular permeability and decreased blood flow (202,203). Corticosteroids may also reduce the release of preformed and newly generated mediators, such as histamine, tryptase, prostanoids, and leukotrienes (204–206). Corticosteroids also inhibit local IgE production and granulocyte levels in the mucosa (207). With the exception of their sterol D rings, all intranasal corticosteroids have common structural elements used in the treatment of inflammation.

At the present time, there are several nasal corticosteroids available to treat AR. These include beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, mometasone furoate, and triamcinolone acetonide. All intranasal steroids are US Food and Drug Administration (FDA) approved for the treatment of AR over 6 years of age. All intranasal steroids were pregnancy category C, with the exception of budesonide, which was FDA pregnancy category B (208). In 2015, the FDA stopped using letter grades for pregnancy recommendations.

Intranasal corticosteroids offer improved efficacy over other classes of medications for AR, and despite variations in their sensory attributes (e.g., taste or smell), there is no evidence of superior clinical response of one agent over another (209,210). With the exception of beclomethasone dipropionate, all other intranasal corticosteroids are quickly metabolized to less active metabolites, have minimal systemic absorption, and have been associated with few systemic side effects (91). The total bioavailability of intranasal mometasone is 0.1% and that of fluticasone propionate is 2% (211). The bioavailability of fluticasone furoate

is 0.5% (212). The bioavailabilities of intranasal triamcinolone acetonide and beclomethasone dipropionate are unknown at this time. Unlike other intranasal corticosteroids, beclomethasone dipropionate is metabolized to active and relatively inactive metabolites, beclomethasone-17-monopropionate and beclomethasone-21 monopropionate and beclomethasone, respectively (213,214). Ciclesonide is a prodrug that is enzymatically converted to the active molecule desciclesonide that has an affinity for the glucocorticoid receptor that is 120 times higher than the parent compound (91). Desciclesonide is 99% protein bound, and there is a high first-pass effect that contributes to desciclesonide's undetectable bioavailability (215).

There have also been promising results using combined therapy of intranasal corticosteroid and intranasal antihistamine. A novel formulation contains azelastine hydrochloride and fluticasone propionate and is delivered as a single nasal spray (216). It is indicated for the treatment of moderate-to-severe SAR and PAR when monotherapy with either an intranasal antihistamine or an intranasal corticosteroid is not sufficient. This combination has shown superior efficacy compared to intranasal antihistamine or intranasal corticosteroid monotherapy for both nasal and ocular symptom relief in AR patients, regardless of disease severity. Additionally, it provided more effective and rapid symptom relief compared with azelastine hydrochloride or fluticasone propionate monotherapy when delivered in the same formulation and device (217).

Recommended doses of intranasal corticosteroids are generally not associated with clinically significant systemic side effects. Studies in children and adults have not demonstrated clinically relevant effects from intranasal corticosteroids on the hypothalamic–pituitary–adrenal (HPA) axis, ocular pressure or cataract formation or bone density. Studies with intranasal beclomethasone demonstrate no effect on the HPA function in adults (218). In children, growth effect may be a better indicator of systemic effect than HPA axis suppression. When compared with placebo, osteocalcin, a marker of bone turnover, and eosinophilia were unaffected by a variety of intranasal corticosteroids, suggesting an insignificant systemic glucocorticoid burden (219). Also, there was no increased risk of bone fracture in octogenarians using intranasal corticosteroids regardless of the dose (220).

There is insufficient data to draw definitive conclusions about the effects of intranasal corticosteroids in the eyes. Intranasal steroids should be used with caution in individuals with glaucoma or cataracts because they may increase risk for exacerbations (221). There have been reports of a possible association

between the development of posterior subcapsular cataracts and the use of intranasal or inhaled corticosteroids in older patients, but this was not confirmed by other studies with intranasal corticosteroids (222,223). A retrospective chart review study of 12 patients showed an increase in intraocular pressure with the use of intranasal corticosteroids, and there were significant reductions in intraocular pressures after discontinuing these topical steroids (224). Another study showed similar effects on intraocular pressure with the use of intranasal or inhaled beclomethasone dipropionate (225).

In children, concerns arose about possible adverse effects of intranasal corticosteroids on growth rate. When beclomethasone was given at twice the recommended dosage, growth suppression was detected in children with PAR (226). Similar studies with fluticasone propionate, mometasone furoate, triamcinolone, and budesonide demonstrated no growth suppression in children when compared with placebo (226–229). A recent study also showed that fluticasone furoate administered over 52 weeks in prepubescent children resulted in a small reduction in growth velocity compared with placebo (230).

Long-term use of intranasal corticosteroids does not appear to cause significant risk for adverse morphologic effects in the nasal mucosa. In a 1-year study of patients with perennial rhinitis treated with mometasone, nasal biopsy specimens showed a decrease in focal metaplasia, no change in epithelial thickness, and no sign of atrophy (231). In another study of intranasal corticosteroid treatment in 90 patients with perennial rhinitis, nasal biopsy specimens revealed normalization of the nasal mucosa at the end of the 12-month study period (232).

The major side effects of intranasal corticosteroids include local dryness or irritation in the form of stinging, burning, or sneezing (91). Local adverse effects of long-term topical intranasal corticosteroids include mucosal irritation that causes discomfort, mild bleeding, dryness, or rarely septal perforation, warranting periodic examination of the nasal cavity (233). Hemorrhagic crusting and perforation of the nasal septum are more common in patients who improperly point the spray toward the septal wall. Patients should be instructed to direct sprays away from the nasal septum to avoid these side effects. This complication may be reduced by tilting the head downward, using a mirror when spraying into the nose, using the new actuators for nasal sprays, and having the right hand spray the device into the left nostril and the left hand spray the device into the right nostril (91). The risk of perforation is usually greatest during the first 12 months of treatment, and the majority of cases involve young women

(234). The development of aqueous formulations has reduced the incidence of local irritation with intranasal corticosteroids, resulting in greater use in children (91).

Initially, some patients may require topical decongestants before administering intranasal corticosteroids. In some cases, a 3- to 5-day course of oral steroids is required to allow delivery of the intranasal corticosteroids in subjects with severe nasal congestion (91). Unlike decongestant nasal sprays, intranasal corticosteroids may be used prophylactically because the maximum benefit is not immediate and may take weeks. Although intranasal corticosteroids may have a delayed onset of action, many patients may have a clinically evident onset of action during the first day of administration (235–237). Intranasal fluticasone dipropionate delivered on an as-needed basis has been shown to be more effective than as-needed H_1-receptor antagonists in the treatment of SAR (238). Although some studies suggest using intranasal corticosteroids on an as-needed basis, optimal effectiveness for patients may be achieved only with regular use (239,240).

Intranasal Corticosteroid Injection

The first report of intranasal corticosteroid injections was in 1951 (241). Intranasal corticosteroid injections are occasionally used in the management of patients with common allergic and nonallergic nasal conditions, such as nasal polyposis; they are not indicated for AR (91). In 2007, a study by Becker et al. (242) demonstrated that intrapolyp steroid injections are associated with a significantly lower rate of complications than surgical excision of sinonasal polyps and may decrease the need for further surgical intervention for polyps. However, this technique has decreased in recent years with the advent of newer and safer topical intranasal steroids and because of possible systemic effects from steroid injections. Two major adverse effects that are seen in turbinate steroid injections but not with intranasal corticosteroid sprays include adrenal suppression secondary to absorption of the steroid and absorption of steroid emboli, which may lead to transient or permanent loss of vision (91).

Systemic Corticosteroids

Oral corticosteroids have greater potency than topical corticosteroids and are an effective treatment for AR. Although AR is not life threatening, it may seriously impair the quality of life, and some patients may only be able to respond to corticosteroids. In addition, oral corticosteroids may be indicated when topical corticosteroids are not adequately distributed in AR patients with marked nasal

obstruction or nasal polyposis. In such cases, a short 5- to 7-day burst of systemic corticosteroids may be indicated, but should be limited to sporadic use. The dose is up to 0.5 mg/kg/day of prednisone or its equivalent. The improvement in nasal symptoms may then be maintained with daily topical intranasal corticosteroids. Oral corticosteroids should be limited in long-term use for AR because of side effects and potential complications associated with its prolonged use (198). Patients who have long-term, systemic dosing of oral corticosteroids often require bone density and blood glucose monitoring and ophthalmic examinations (208). It is essential for clinicians and patients to weigh the risks and benefits of oral corticosteroid use in deciding systemic dosing frequency, amount, and treatment duration.

Antihistamines

Antihistamines are useful for the management of intermittent AR, mild AR, SAR, or PAR. Antihistamines are most useful in controlling the symptoms of sneezing, rhinorrhea, and pruritus that occur in AR. Antihistamines are compounds of varied chemical structure that have the property of antagonizing some of the actions of histamine.

The first-generation antihistamines (e.g., chlorpheniramine, diphenhydramine, tripelennamine, and clemastine fumarate) are effective H_1-receptor antagonists. Problems associated with their use relate to side effects, which are numerous and can be severe in some patients. The most common and most important effects are anticholinergic, including dry mouth and eyes, urinary retention, and central nervous system (CNS) effects (primarily sedation, and impairment of motor and cognitive functions). The patient may not be aware of having reduced cognitive ability, because it can occur independently of sedation (243). Recent meta-analyses found significant overuse of anticholinergic agents, including antihistamines in cognitively impaired individuals, preventing them from attending memory clinic. Therefore, special care should be taken when prescribing sedating antihistamines to elderly patients, especially if they are at risk for cognitive impairment (244–248). Large doses of first-generation antihistamines, such as diphenhydramine, are rarely reported to cause torsades de pointes. Populations that require caution are those taking more than one antihistamine, patients with hypertension who require a diuretic, patients with hypokalemia or hypomagnesemia, and patients taking antiarrhythmic agents (248). The CNS side effects can be problematic in any patient, particularly those who need to drive motor vehicles or operate complex machinery, or pay attention and learn in school. Often underrecognized are the potentiating effects

of alcohol and other CNS depressing drugs, such as sedatives, hypnotics, and antidepressants.

Because the newer second-generation antihistamines do not appreciably penetrate the blood–brain barrier, most studies show a lack of sedation. These medications are free of anticholinergic side effects, such as dry mouth, constipation, difficulty voiding, and blurry vision. Older patients, who may have benign prostatic hypertrophy or xerostomia, usually tolerate these drugs. Because fatal cardiac arrhythmias occurred when terfenadine and astemizole were given concomitantly with erythromycin (a macrolide antibiotic), imidazole antifungal agents (ketoconazole and itraconazole), or medications that inhibit the cytochrome P450 system (249,250), these drugs have been removed from the US market. The other second-generation antihistamines, such as loratadine, desloratadine, fexofenadine, cetirizine, and levocetirizine, have not been associated with cardiac toxicity. The second-generation antihistamines have a rapid onset of action that allows them to be taken as needed (91).

Azelastine, available as a nasal spray, is a selective H_1-receptor antagonist with structural and chemical differences that distinguish it from currently available antihistamines (91). Azelastine is 10 times more potent than chlorpheniramine at the H_1-receptor site (251). In addition to this H_1-blocking action, azelastine has demonstrated an inhibitory response on cells and chemical mediators of the inflammatory response. Azelastine prevents leukotriene generation from mast cells and basophils, and modulates the activity of eosinophils and neutrophils, macrophages, and cytokines (91). Azelastine has a low incidence of somnolence and does not seem to result in psychomotor impairment. Azelastine is indicated for both SAR and PAR and can be considered first-line treatment for mild SAR and PAR because the medication has a rapid onset of action of approximately 30 minutes. Azelastine also has efficacy in moderate-to-severe AR (91). Combined therapy of intranasal azelastine and fluticasone has been shown to be more effective than either monotherapy alone. A recent study found that intranasal azelastine had comparable efficacy to intranasal fluticasone in the treatment of moderate-to-severe SAR (252). Olopatadine nasal spray is a selective H_1-receptor antagonist and, like azelastine, has a fast onset of action (253), and has shown efficacy in SAR. An unpleasant taste is the most common side effect of both azelastine and olopatadine, but overall, they are well tolerated (254).

Sympathomimetic Agents

Sympathomimetic drugs are used as vasoconstrictors for the nasal mucous

membranes and may be used in combination with oral antihistamines; however, studies failed to show improved benefit compared to either as monotherapy (255). Pseudoephedrine is generally reported to be more effective than phenylephrine. The adverse effect profile of decongestants includes insomnia, anorexia, and irritability. Oral decongestants should be avoided in children less than 4 years of age, elderly adults, and any patient with a history of cardiovascular disease or hyperthyroidism. *RM* may occur within 3 days of intranasal vasoconstrictor use although in some patients may not develop until 6 weeks of use (256). The recommendation is to limit use to less than 3 days.

Leukotriene-Receptor Antagonists

Leukotrienes are newly formed mediators that have been found to be important in allergic disease. The inhibition of LTC_4, $LTCD_4$, and $LTCE_4$ or 5-lipoxygenase has been an important strategy for management of AR and asthma. Leukotriene-receptor antagonists, montelukast and zafirlukast, have been reported to be effective for the treatment of AR. Studies have demonstrated similar efficacy of montelukast to a second-generation oral antihistamine, and in certain patients, there might be an additive effect when combined with an antihistamine (257–261). A meta-analysis demonstrated that, as compared with placebo, montelukast induced a moderate but significant reduction in scores for daily symptoms of rhinitis. In comparison, nasal corticosteroids induced a significant and substantial reduction in symptom scores (259). Thus, the role of montelukast is generally as an adjunct in the treatment of a patient who does not have an adequate response to an antihistamine or a nasal corticosteroid or both. However, there are no clear data demonstrating that leukotriene-receptor antagonists combined with either antihistamines or nasal corticosteroids reduce symptom scores more than the antihistamines or corticosteroids alone. Leukotriene-receptor antagonists, however, have shown efficacy in aspirin-sensitive rhinitis (262) and in patients who have the combination of SAR and mild asthma (263).

Anticholinergics

Parasympathetic fibers originate in the superior salivatory nucleus of the brainstem, and relay in the sphenopalatine ganglion before distributing to the nasal glands and blood vessels. Parasympathetic stimulation causes a watery secretion, mediated by the classical autonomic transmitter acetylcholine, and a vasodilatation of blood vessels serving the glands. The muscarinic receptors of the seromucinous glands can be blocked by the anticholinergic drug, ipratropium bromide. Ipratropium bromide, a quaternary derivative of isopropyl noratropine,

is poorly absorbed by the nasal mucosa because of a low-lipid solubility and does not cross the blood–brain barrier. Ipratropium bromide is effective in controlling watery nasal discharge, but it does not affect sneezing or nasal congestion in both PAR and NAR. The drug is effective for the treatment of common cold (264), gustatory rhinitis, and rhinorrhea in elderly patients. One study demonstrated that atropine sulfate, a nonselective muscarinic receptor antagonist, improved severe rhinorrhea in patients with PAR, whereas the other nasal symptoms were not improved significantly (265). Topical side effects, caused by anticholinergic action, are uncommon and usually dose dependent in their severity. Nasal dryness, irritation, and burning are the most prominent effects, followed by a stuffy nose, dry mouth, and headache. Because patients with perennial rhinitis usually suffer also from nasal congestion, itching, and sneezing, other drugs are preferable as first-line agents to ipratropium in the vast majority of cases of AR. Ipratropium combined with an intranasal glucocorticosteroid or an H_1 antihistamine may be considered in patients where rhinorrhea is the predominant symptom, or in patients with rhinorrhea who are not fully responsive to other therapies.

Intranasal Cromolyn

In the United States, cromolyn nasal spray is available without prescription, has minimal systemic absorption, and is very safe for chronic use without evidence of tachyphylaxis (150). The main clinical disadvantage of intranasal cromolyn is the need for administration four to six times per day for ongoing treatment effect (92). The proposed mechanism of action of cromolyn in AR is to stabilize mast cell membranes, apparently by inhibiting calcium transmembrane flux and thereby preventing antigen-induced degranulation. It is effective in the management of both SAR and PAR. Cromolyn can be effective in reducing sneezing, rhinorrhea, nasal pruritus, and in a limited number of patients with nasal polyps. It has little effect on mucociliary transport. Cromolyn often prevents the symptoms of both SAR and PAR, and diligent prophylaxis can significantly reduce both immediate and late symptoms after allergen exposures.

Adverse effects are rare and mostly include sneezing, nasal stinging, nasal burning, transient headache, and an unpleasant aftertaste. For management of seasonal rhinitis, treatment should begin 2 to 4 weeks before contact with the offending allergens, and should be continued throughout the period of exposure. Because cromolyn has a delayed onset, concurrent antihistamine therapy is usually necessary to control symptoms. It is essential for the patient to understand the rate and extent of response to be expected from intranasal

cromolyn, and that because the product is prophylactic, it must be used on a regular basis for maximum benefit.

Capsaicin Nasal Spray

Capsaicin is a pungent agent derived from red peppers that is known for desensitizing peptidergic sensory C fibers and reducing nasal hyperreactivity. It is most well studied in NAR and is available without a prescription (147). In a randomized study of 42 patients with AR and NAR, intranasal capsaicin and eucalyptol were used twice daily for 2 weeks compared with placebo (266). There was a statistically greater reduction in total nasal symptom score, with greatest improvements in nasal congestion, sinus pressure, and headache. There was no reduction in sneezing, rhinorrhea, and postnasal drip between the active and placebo groups. New agents targeting these same nasal sensory receptors may potentially control nasal hyperreactivity that underlies AR and NAR.

Complementary and Alternative Therapies

Acupuncture

Acupuncture is a component of traditional Chinese medicine that works on the principle of redistribution of Qi, the life energy. Acupuncture may exert its anti-inflammatory effect through the HPA axis or by the sympathetic and parasympathetic nervous systems. Additionally, other anti-inflammatory properties include a histamine antagonist effect and downregulation of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6, and IL-10), pro-inflammatory neuropeptides (e.g., substance P), cGRP, VIP, neurotrophins (e.g., nerve growth factor [NGF] and brain-derived neuronal factor [BDNF]), and the expression of COX-1, COX-2, and nitric oxide synthase (267). A recent systematic review of 13 studies evaluated 2,365 AR patients (1,126 treated versus 1,239 placebo). The group receiving acupuncture experienced a significant reduction in nasal symptom scores. A nonsignificant trend was found for relief medication scores, and no effect was observed for the rhinitis quality of life questionnaire (RQLQ). No serious adverse effects were observed for the acupuncture treatment group (268). An additional trial reported that 175 patients who received acupuncture had decreased sneezing and pruritic symptom scores and improvement in RQLQ scores (269). Acupuncture is a reasonable option for individuals with mild AR disease who wish to minimize pharmacologic therapy. However, although acupuncture may cause small improvement in symptom quality of life, it is very expensive and may not be a cost-effective treatment of AR (270).

Acupressure

Acupressure is similar to acupuncture without involvement of needles. In an Australian trial, 63 SAR patients were randomly assigned to real ($n = 31$) and sham ($n = 32$) ear acupoint groups for a total of 8 weeks. Total nasal symptoms score and regular activities at home and work were significantly improved in the real compared with the sham ear acupoint groups (271). A follow-up study investigated 245 PAR patients randomized to receive real or sham ear acupressure treatment once weekly for 8 weeks with a 12-week follow-up period. There was a small, statistical improvement in sneezing and quality of life along with additional improvements in most measures of nasal symptoms at the end of the follow-up period in the acupressure group compared to the sham group (272). These studies demonstrate a significant effect of ear acupressure on AR. Additional studies will be required to make more definitive recommendations about the utility of this therapy.

Rhinophototherapy

Similar to phototherapy that treats various inflammatory skin diseases, including atopic dermatitis, rhinophototherapy may also act as an immunosuppressive agent to treat AR. A randomized, double-blind, placebo-controlled study was conducted to assess the effect of rhinophototherapy in 49 ragweed SAR patients during their peak season, using a combination of ultraviolet (UV)-B (5%), UV-A (25%), and visible light (70%). Rhinophototherapy resulted in a significant improvement in total nasal symptoms score, sneezing, rhinorrhea, and nasal itching compared to the control group. Additionally, the nasal lavage studies revealed a significantly reduced number of eosinophils, ECP, and IL-5 (273). Two months after completion of therapy, cytology samples showed that any UV damage to the nasal mucosa induced by intranasal phototherapy is resolved (274). In an uncontrolled study, the addition of phototherapy to mometasone resulted in improvement of symptom and RQLQ symptom scores compared to the mometasone monotherapy group (275). Despite no direct data on the effect of phototherapy in AR, there is limited data that point to a reduction of symptoms and eosinophil counts in AR.

Intranasal Carbon Dioxide (CO_2)

Intranasal CO_2 may inhibit trigeminal neuronal activation and suppress the release of cGRP that are both increased in rhinitis. A randomized, double-blind, placebo-controlled study evaluated two 60-second intranasal treatments with CO_2 which resulted in rapid (within 10 minutes) and sustained (up to 24 hours)

relief of SAR symptoms (276).

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Nasal Polyposis, Rhinosinusitis, and Nonallergic Rhinitis

TOLLY G. EPSTEIN AND DAVID I. BERNSTEIN

◾ NASAL POLYPS

Nasal polyps have been recognized and treated since ancient times. The occurrence of nasal polyps in association with asthma and aspirin sensitivity, sometimes known as the "aspirin triad," was first identified in 1911 (1). The aspirin triad is now called aspirin-exacerbated respiratory disease (AERD) (2). Nasal polyps are associated with chronic mucosal inflammation—a condition often referred to as chronic hyperplastic rhinosinusitis. In most cases, nasal polyps arise from the mucosa of the middle meatus and clefts of the ethmoid region (2,3). Polyp tissue is generally characterized by chronic, eosinophilic infiltration, but plasma cells, lymphocytes, and mast cells are also typically present (4,5). Polypoid tissue is rich in ground substance-containing acid mucopolysaccharide (6).

The prevalence of nasal polyposis in the general population is estimated at 2% to 4% (7,8). A large population-based study did not reveal any gender differences, but there are reports of male predominance (2,9). Nasal polyps are diagnosed more often during the third and fourth decades of life. Most clinical data indicate that there is no greater prevalence of nasal polyps among atopic compared with normal populations; however, the coexistence of allergic rhinitis may render symptom control more challenging (10,11). In a study of an adult allergy clinic population, 4.2% of patients had nasal polyps; 71% of polyp patients had asthma, and 14% had aspirin intolerance (12). Nasal polyps are less common in children. The discovery of nasal polyps in a child, especially in association with nasal colonization by *Pseudomonas* species, should prompt an evaluation for cystic fibrosis (CF), in which the prevalence of nasal polyps is 6.7% to 48% (13–15). Nasal polyps are also reported to affect 37% of adults with CF (16).

Clinical Presentation

Patients with nasal polyposis present with perennial nasal congestion, rhinorrhea, and anosmia (or hyposmia). Nasal and ostiomeatal obstruction may result in purulent nasal discharge and chronic sinusitis. Enlargement of nasal polyps may lead to broadening of the nasal bridge. Rarely, encroachment into the orbit can occur, resulting in compression of ocular structures and unilateral proptosis, falsely suggesting an orbital malignancy (17,18).

A thorough nasal examination, preferably with a nasal speculum, is necessary for identification of nasal polyps. More complete visualization can be accomplished by flexible rhinoscopy. Nasal polyps appear as bulbous translucent to opaque growths, often extending from the middle and inferior nasal turbinates, causing partial or complete obstruction of the nasal canals. Frontal, ethmoidal, and maxillary tenderness with purulent nasal discharge from the middle meatus indicate concurrent acute or chronic paranasal sinusitis. Sinus imaging studies are rarely needed to identify nasal polyps. Common imaging changes include widening of the ethmoid labyrinths, mucoceles or pyoceles within the paranasal sinuses, and generalized loss of translucence in the maxillary, ethmoid, and frontal sinuses (17). Sinus imaging is reviewed in detail in Chapter 10.

Causes

Although multiple theories regarding the etiology of nasal polyposis have been proposed, the pathogenesis remains poorly defined. Allergic mechanisms have been investigated, but no consistent association has been established between atopy and nasal polyposis. Patients with nasal polyps are less likely to be sensitized to perennial allergens than those diagnosed with allergic rhinitis (19). Mast cells and mast cell mediators are abundant in polyp tissue. T_H2-directed inflammation is suggested by the presence of abundant eosinophils in 70% to 90% of cases (4). $CD8^+$ T cells are increased in polyp tissue when compared with healthy controls (20).

Growth factors and cytokines that can stimulate $in \ vitro$ proliferation of basophils, mast cells, innate lymphoid type 2 cells, and eosinophils are present in nasal polyp tissue (21–23). The potential roles of T_H1 (T-helper cell type 1) and T_H2 (T-helper cell type 2) cytokines are under investigation (24). Total immunoglobin E (IgE) and interleukin 5 (IL-5) levels are higher in nasal tissue of patients with chronic rhinosinusitis (CRS) and nasal polyps, compared with CRS patients without polyps (25). Overproduction of thymic stromal lymphopoietin may enhance T_H2 inflammation in nasal polyp tissue (23). The pathophysiology of CF-related polyp disease may be different from that of non–

CF-related polyps. For example, myeloperoxidase and IL-8 are increased in polyp tissue from CF patients, whereas eosinophilic cation protein, eotaxin, and IgE are frequently elevated in nasal polyps of patients without CF, especially in those with aspirin sensitivity and/or asthma (26,26a).

Microbial pathogens have been postulated to play roles in the pathogenesis of nasal polyps by promoting inflammation. In particular, *Staphylococcus aureus*–derived toxins may act as conventional allergens, leading to the production of specific IgE (sIgE), or as superantigens that can nonspecifically activate T cells (27). Treatment with antibiotics effective against *S. aureus* has shown some efficacy (28).

The role of oxidative stress has also been investigated. Free oxygen radicals have been identified in nasal polyp tissue. Increased severity of nasal polyposis and bronchial hyperresponsiveness correlate with levels of free oxygen radicals in polyp tissue (29,30).

AERD is generally associated with severe nasal polyposis and chronic sinusitis that is less responsive to treatment (31,32). The link between aspirin sensitivity, asthma, and nasal polyps has been attributed to reduced prostaglandin E_2 and enhanced the production of leukotrienes from arachidonic acid. Patients with nasal polyposis generally have elevated levels of urinary leukotriene E_4 (LTE_4) at baseline (33). Aspirin-sensitive patients demonstrate increased levels of urinary LTE_4 after oral aspirin challenge (34). In addition, LTC_4 synthase is overexpressed in nasal polyps of patients with AERD (35).

Treatment

Intranasal glucocorticoids are the treatment of choice for nasal polyposis and are more effective long term than surgical polypectomy (36). Intranasal steroids significantly reduce polyp size, nasal congestion, rhinorrhea, and increase nasal airflow (37–39). Aggressive treatment of nasal polyps with intranasal corticosteroids has also been shown to reduce the need for surgery (40). The effectiveness of intranasal steroids on improving olfactory dysfunction is variable (41,42). Optimal results may require a short course of oral corticosteroids (30 to 35 mg of prednisone daily for 5 to 7 days), followed by maintenance therapy with intranasal steroids (43–45). In a controlled trial, a course of oral steroids significantly reduced hyposmia and size of nasal polyps (44). Patients should be instructed to avoid the nasal septum when administering nasal steroids in order to limit irritation. Higher doses of intranasal corticosteroids may be more effective, although a recent *Cochrane Database*

Review found insufficient evidence that one type of nasal steroid is superior to another (46,47). Fluticasone propionate administered as 400 μg twice daily was more effective than 400 μg once daily in improving nasal inspiratory flow and reducing polyp size (38). Coexistent sinus infections, which may reduce responsiveness to intranasal steroids, should be treated appropriately.

Leukotriene antagonists may provide a modest benefit as an adjunctive treatment along with nasal steroids. In a double-blind study of 40 postoperative patients with nasal polyps, there was no difference in the recurrence rate of polyps between patients treated with montelukast versus nasal beclomethasone for 1 year (48). However, intranasal steroids exhibited superiority in treating olfactory deficits and nasal congestion. Another small, double-blind study found significant improvement in Health-related-Quality-of-Life in polyps patients on montelukast versus placebo for 4 weeks (49). A small study suggested that Zileuton, a 5-lipoxygenase inhibitor, may be more effective than other leukotriene antagonists for nasal polyps, but larger, controlled trials are needed (50).

Surgical treatment for nasal polyposis should be considered when optimal medical therapy has failed. Simple polypectomy may be indicated for complete nasal obstruction, which causes extreme discomfort. If nasal polyps are associated with persistent ethmoid sinusitis with obstruction of the ostiomeatal complex, a more extensive surgical procedure may be considered. Several randomized controlled trials have shown equivalent outcomes at 1 year of follow-up after surgical versus medical management of nasal polyps (51,52). Nasal polyps frequently recur after simple surgical polypectomy, and long-term recurrence rates may be as high as 60% following functional endoscopic sinus surgery (FESS) for severe disease (53). Although further studies evaluating the role of long-term nasal steroids after surgery are needed, their administration in this setting should be considered to prevent recurrence (54,55).

Outcomes of FESS are generally less favorable among aspirin triad patients compared with patients with chronic sinusitis who are aspirin insensitive (56,57). In a retrospective study, patients with aspirin triad had more extensive sinus disease based on radiologic findings, and 39% required surgical revisions versus 9% of sinusitis patients without aspirin sensitivity (56). The addition of aspirin following surgery may improve long-term outcomes in selected patients with nasal polyposis and AERD (58–61). Long-term aspirin desensitization has been reported to reduce the number of episodes of acute sinusitis, corticosteroid use, and requirement for polypectomies and sinus surgery (34,62). Because of the

risk of provoking severe asthmatic attacks, this procedure should be performed exclusively by an experienced practitioner in an appropriate setting, and considered only in aspirin-sensitive patients refractory to conventional therapies (63).

In recent years, research on biologics for nasal polyposis has begun to emerge. Omalizumab, an anti-IgE monoclonal antibody, has beneficial effects in treating nasal polyps, and it can be considered if more conservative medical and surgical treatment are not effective (8,28,64). Although only approved by the Food and Drug Administration for severe eosinophilic asthma, anti-IL-5 monoclonal antibodies, such as mepolizumab and reslizumab, have shown benefit for nasal polyps as well (65,66).

Rhinosinusitis

The term sinusitis is used interchangeably with the term rhinosinusitis (RS), with the later recently accepted as the preferred terminology. RS is classified as acute rhinosinusitis (ARS) (symptoms <12 weeks); recurrent ARS (≥3 episodes of acute bacterial RS in the past year); and CRS (persistent symptoms >12 weeks) (8). CRS can be divided into those with nasal polyps (CRSwNP) and those without nasal polyps (CRSsNP). RS affects approximately 13% to 14% of the population, with 20,000 cases of acute bacterial sinusitis each year (8,67,68). The estimated annual health care costs for acute sinusitis exceed $3.5 billion annually, and the annual costs of CRS are estimated at $8 billion (8,69,70). RS is an inflammatory disorder of the mucosal lining of the nose and paranasal sinuses that may be initiated by infectious or noninfectious factors. Viral upper respiratory infections often precede acute bacterial sinus infections. Given that most viral infections resolve within 7 to 10 days, acute bacterial sinusitis is typically suspected when symptoms persist or worsen beyond 10 days with facial pain, postnasal drip, and purulent discharge (8,71).

Noninfectious triggers for RS include environmental exposures to fumes or chemical vapors. ARS has long been considered a complication of seasonal or perennial allergic rhinitis (72–74). Individuals with exposure to tobacco smoke and those with nonallergic rhinitis are also more susceptible to recurrent or chronic sinusitis (75–77).

Regardless of initiating events, the four physiologic derangements that contribute to the evolution of infectious sinusitis are: (a) reduced patency of the sinus ostia; (b) a decrease in the partial pressure of oxygen within the sinus cavities; (c) diminished mucociliary transport; and (d) compromise of

microcirculation blood flow in the mucosa (78,79). Edematous obstruction of the sinus ostia is a consistent finding in both acute and chronic sinusitis; this condition causes a low-oxygen environment within the sinus cavity, which results in decreased mucociliary transport and favors the growth of common bacterial pathogens, including *Streptococcus pneumoniae, Haemophilus influenzae,* and anaerobic bacteria (80,81).

Studies suggest there are different CRS phenotypes or endotypes based on the presence or absence of infection or predominance of neutrophils or eosinophils; characterization of patient phenotypes may in the future guide treatment strategies (82,83). Patients presenting with noninfectious CRS (with or without AERD) and nasal polyposis exhibit predominant eosinophilic infiltration associated with increased expression of type 2 mediators, including IL-5, IL-13, and eotaxin-2, as compared to CRS patients without nasal polyps (84). The eosinophilia associated with nasal polyps may be more common in those of European descent; neutrophilia may be predominant in nasal polyp tissue of Asians (82).

Causative Microorganisms

Microbial pathogens implicated in ARS have been studied extensively. Identification of bacterial pathogens by endoscopically directed middle meatal cultures closely approximates results obtained via needle puncture of the maxillary sinus (85,86). Cultures obtained by middle meatal sampling or maxillary sinus puncture for acute bacterial sinusitis in adults revealed that the most common pathogens are *S. pneumoniae, H. influenzae, S. aureus,* and *Moraxella catarrhalis* (87). Another study of 339 adult patients with acute sinusitis found that viruses were cultured from 8% of aspirates, whereas 15% to 40% of antral aspirates were sterile. Common isolates included rhinovirus, influenza type A, and parainfluenza viruses (88).

In children with acute maxillary sinusitis, *S. pneumoniae, H. influenzae,* and *M. catarrhalis* have been identified as the predominant pathogens (89). Since the introduction of the pneumococcal conjugate vaccine (PCV13), the proportion of sinusitis caused by *S. pneumoniae* has declined, whereas that caused by *H. influenzae* has increased (8,90,91). Viruses were isolated from 4% of pediatric patients in one study, and 20% of cultured aspirates were sterile (88). Anaerobic bacteria play a large role in CRS in adults, but are rarely identified in children. There is also increasing concern for drug-resistant Gram-negative organisms in chronic sinusitis, particularly *Pseudomonas aeruginosa* (92,93).

Immunocompromised individuals may develop invasive forms of fungal sinusitis involving unusual or opportunistic organisms. Invasive fungal RS should be suspected with opacified sinuses with soft tissue infiltration and/or osseous destruction (8). Mucormycotic sinusitis is caused by fungi of the family Mucoraceae (Mucor), which are zygomycetes, and may be isolated from the throat and stools of normal individuals (94). Mucormycotic sinusitis is potentially fatal in diabetic, leukemic, or otherwise immunosuppressed patients (95). Invasive aspergillosis involving the sphenoid sinus is particularly difficult to treat, even in immunocompetent patients, and can result in severe neurologic complications (96). Rarely, tuberculosis can cause infectious sinusitis, particularly in immunocompromised patients (97). Atypical mycobacteria have been reported to cause sinusitis in patients with acquired immunodeficiency syndrome (98).

Allergic fungal sinusitis is an increasingly recognized syndrome occurring in immunocompetent atopic patients with hypertrophic rhinitis and nasal polyps. Abundant mucin found within the sinuses demonstrates numerous eosinophils and Charcot–Leyden crystals; fungal stains reveal the presence of noninvasive hyphae (99,100). The disease occurs primarily in adults, but should be considered in atopic children with refractory sinus disease (101). Although *Aspergillus* species are frequently involved, dematiaceous fungi have also been implicated. In particular, *Bipolaris spicifera* plays a prominent role in the Southwest region of the United States (102). Patients generally exhibit high total serum IgE levels and have positive skin tests to fungal allergens (100,103).

Clinical Presentation

Episodes of bacterial ARS are most commonly preceded by symptoms suggestive of viral upper respiratory tract infections or other environmental stimuli, which can cause mucosal inflammation, hypertrophy, and obstruction of the sinus ostia. Common presenting symptoms include frontal or maxillary head pain, fever, and mucopurulent or bloody nasal discharge lasting longer than 7 to 10 days. Other clinical features include general malaise, cough, hyposmia, mastication pain, and changes in the resonance of speech. Pain cited as coming from the upper molars may represent an early symptom of acute maxillary sinusitis. Children with acute maxillary sinusitis present most often with cough, nasal discharge, and fetid breath; fever is less common (89).

Symptoms associated with CRS are less fulminant; facial pain, headache, and postnasal discharge are common symptoms (8). The clinician should be aware

that chronic maxillary sinusitis may result from primary dental infections (i.e., apical granuloma of the molar teeth, periodontitis) (88). Pain associated with temporomandibular dysfunction may be incorrectly diagnosed as chronic sinusitis. Individuals with sinusitis may experience severe facial pain associated with rapid changes in position (e.g., lying supine or bending forward) or with rapid changes in atmospheric pressure that occur during air travel.

Episodes of ARS or CRS may be manifestations of other underlying problems. Local obstruction by a deviated nasal septum, nasal polyps, or occult benign or malignant neoplasm may explain recurrent sinus infections. Patients presenting with frequent CRS exacerbations or recurrent ARS that responds poorly to antibiotics or surgical treatment should be examined for primary or acquired immunodeficiency states (8). Humoral immune deficiencies that should be considered include specific antibody deficiency, common variable immune deficiency, rare complement deficiencies, and selective IgA deficiency in combination with IgG subclass deficiency (104–106). Disorders of ciliary dysmotility may occur in male patients. Kartagener syndrome is characterized by recurrent sinusitis, nasal polyps, situs inversus, infertility, and bronchiectasis (107). Nasal mucosal biopsy and electron microscopic examination to identify abnormalities in ciliary structure should be done in suspected cases. Granulomatosis with polyangiitis is a necrotizing vasculitis that presents with epistaxis, refractory sinusitis, serous otitis, nodular pulmonary infiltrates, and focal necrotizing glomerulonephritis (108). Chronic sinusitis or otitis media can precede pulmonary and renal manifestations for years before full expression of the disease. Early diagnosis and treatment of this systemic vasculitis before development of renal disease can be lifesaving. Eosinophilic granulomatosis with polyangiitis is another disease in the differential of severe CRSwNP (8).

Diagnosis

Palpable tenderness, erythema, and warmth may be appreciated over inflamed frontal, ethmoid, or maxillary sinuses. Persistent purulent rhinorrhea and facial pain predict a high likelihood of bacterial ARS. Sinus imaging should be reserved for patients suspected of acute complication of ARS unresponsive to antibiotics, or patients with CRS for whom anatomic abnormalities are suspected and/or surgical intervention is being considered. Magnetic resonance imaging (MRI) is recommended for patients with persistent symptoms of unilateral CRS to exclude a tumor or soft tissue mass extending to the orbit or into the cranium (8,109). Rhinoscopy can be useful in identifying purulent discharge in the middle meatus compatible with acute maxillary sinusitis (8). Computed

tomography (CT) is particularly useful for defining abnormalities in the anterior ethmoid and middle meatal areas (ostiomeatal unit), which cannot be visualized well on sinus roentgenograms. The CT coronal views (Fig. 27.1) are much less costly than a complete sinus CT and are adequate for determining the patency of the ostiomeatal complex, which includes the ethmoid and maxillary ostia and infundibulum. Demonstration of ostiomeatal obstruction is essential for assessing the need for surgical intervention in patients with CRS (110).

Complications

In the age of antibiotics, severe life-threatening complications of acute sinusitis are relatively uncommon. However, the clinician must be able to recognize clinical manifestations of potentially fatal complications of sinusitis so that medical and surgical treatments can be initiated in a timely manner.
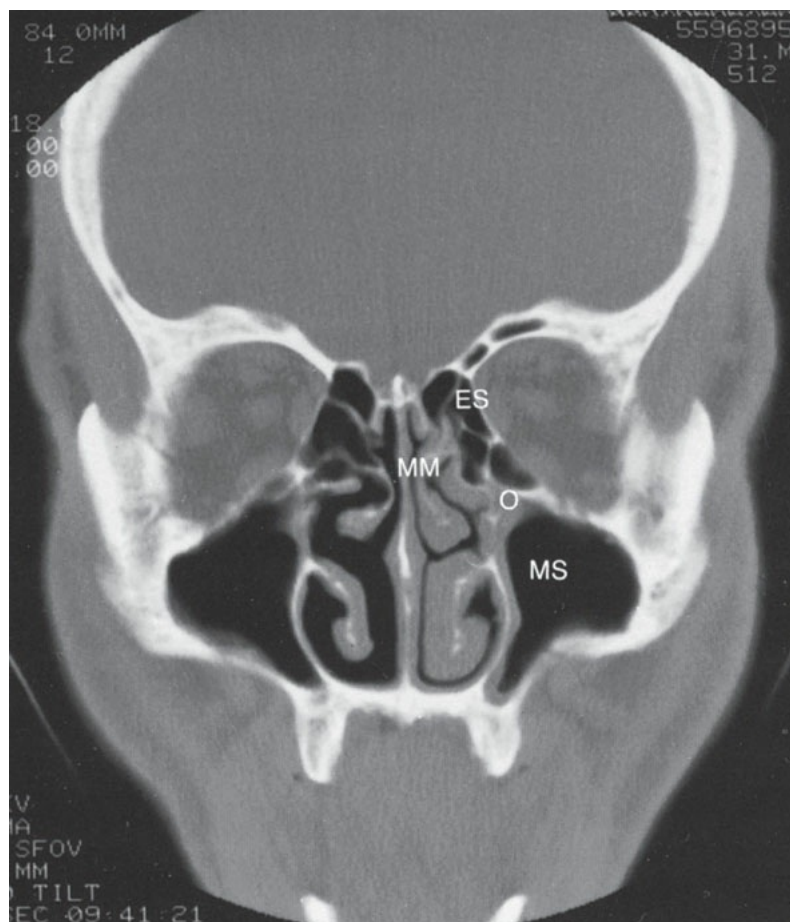
■ **FIGURE 27.1** Computed tomographic image of the paranasal sinuses. A coronal section exhibits significant sinus disease on the left with a relatively normal appearance on the right. The left middle meatus (MM) and maxillary ostium (O) are obstructed by inflamed tissue, causing significant obstruction of the left ethmoid (ES) and maxillary (MS) sinuses.

Serious complications of frontal sinusitis may be attributed to the proximity of the frontal sinus to the roof of the orbit and anterior cranial fossa. Osteomyelitis can result from acute frontal sinusitis and may present as a localized subperiosteal abscess (Pott's puffy tumor) (111). Intracranial complications of frontal sinusitis include extradural, subdural, and brain abscesses as well as meningitis and cavernous sinus thrombosis (112,113). CT scans may be adequate to diagnose some complications of sinusitis, but MRI is superior to evaluate intracranial findings. Acute ethmoiditis is encountered most commonly in children. Extension of inflammation into the orbit can result in unilateral orbital and periorbital swelling with cellulitis. This presentation can be distinguished from cavernous sinus thrombosis by the lack of focal cranial neurologic deficits, absence of retro-orbital pain, and no meningeal signs. Patients with orbital cellulitis usually respond to antibiotics, and surgical drainage is rarely necessary.

Cavernous sinus thrombosis is a complication of acute or chronic sinusitis that demands immediate diagnosis and treatment. The cavernous sinuses communicate with the venous channels draining the middle one-third of the face. Cavernous sinus thrombosis often arises from a subcutaneous infection in the face or paranasal sinuses. Vital structures that course through the cavernous sinus include the internal carotid artery and the third, fourth, fifth, and sixth cranial nerves. Symptoms of venous outflow obstruction caused by cavernous sinus thrombosis include retinal engorgement, retrobulbar pain, and visual loss. Impingement of cranial nerves in the cavernous sinus can result in extraocular muscle paralysis and trigeminal sensory loss. If not treated promptly with high doses of parenteral antibiotics, septicemia and central nervous system involvement can lead to a fatal outcome (114). Surgical intervention may be required.

Acute sphenoid sinusitis is difficult to diagnose. A high index of suspicion and radiologic imaging with CT scan or MRI, are essential (115,116). Affected patients report occipital and retro-orbital pain, or the pain distribution may be nonspecific. Because of the posterior location of the sphenoid sinus, diagnosis of sphenoiditis may be delayed until serious complications are recognized. Extension of infections to contiguous structures may result in ocular palsies, orbital cellulitis, subdural abscess, meningitis, or hypopituitarism.

It has long been recognized that chronic or recurrent sinusitis may exacerbate asthma. There is a strong correlation between sinus mucosal thickening and biomarkers of bronchial inflammation (e.g., sputum eosinophils, exhaled nitric

oxide) in severe asthmatics (117). Surgical treatment of CRS may improve control in patients with difficult or refractory asthma (28,56,118,119).

Treatment of Acute Sinusitis

The primary goal of treatment should be facilitation of drainage of affected sinuses and elimination of causative organisms. Gwaltney et al. studied 31 patients who presented with upper respiratory infection with significant CT abnormalities consistent with sinusitis (120). CT abnormalities spontaneously resolved in most patients 2 weeks later without antibiotics, suggesting that antibiotics are used unnecessarily in many patients. Judicious use of antibiotics is essential, especially in light of increasing problems with antibiotic resistance. Topical nasal vasoconstrictors (e.g., oxymetazoline) used prudently over the initial 2 to 3 days of treatment of acute sinusitis can facilitate drainage. Oxymetazoline and saline lavage used in combination for acute sinusitis have been shown to improve mucociliary clearance (121). The use of nasal steroids either as monotherapy or in combination with antibiotics for acute sinusitis has been advocated (8). A meta-analysis involving patients with radiographic or endoscopically diagnosed acute sinusitis who were not on antibiotics found that nasal steroids were more effective than placebo at relieving symptoms, with greater benefit seen at higher doses (122).

Antibiotics should be considered in those who fail the aforementioned drainage measures, or who have persistent symptoms for more than 7 to 10 days. The emergence of penicillin-resistant strains must be recognized. For treating bacterial ARS, amoxicillin-clavulanate given for 14 days is recommended as the empiric antibiotic of choice in both adult patients and children (91). For those suspected of penicillin allergy, doxycycline (in adults), levofloxacin, and moxifloxacin are recommended as alternative agents (91). Owing to concerns over antibiotic resistance, macrolide antibiotics are no longer recommended for bacterial ARS. Treatment failures for acute sinusitis are not uncommon. Parenteral antibiotics should be instituted if local extension of infection (i.e., cellulitis or osteomyelitis) occurs, or if the infection is suspected to have spread to vital ocular or central nervous system structures. Surgical drainage of infected sinuses may be indicated when fever, facial pain, and sinus imaging changes persist, and for complicated cases of acute sinusitis. FESS may be superior to open techniques, depending on the specifics of a particular case (123). For patients with acute maxillary sinusitis who do not respond to conservative (medical) drainage measures and aggressive antibiotic therapy, antral puncture and irrigation may be indicated; ostial dilatation with a balloon is an alternative

approach (8). Similar principles apply to the treatment of frontal, ethmoid, or sphenoid sinusitis.

Treatment of Chronic Rhinosinusitis

The treatment approach to CRS and recurrent exacerbations should begin with identifying modifiable factors, such as allergic rhinitis, deviated nasal septum, nasal polyps, concha bullosa, exposure to tobacco smoke, toxic irritants at work, and other environmental factors. Acute exacerbations of CRS can be treated with short-term antibiotics, but there is no good evidence to support chronic antibiotic treatment for CRS (8). A course of oral steroids alone or combined with antibiotics may be effective in treating worsening CRS symptoms, especially in CRSwNP. One study showed improvements in nasal symptoms and nasal inspiratory flow in CRS patients treated with intranasal budesonide for 20 weeks (124). Chronic treatment with daily nasal irrigation is a very useful adjunctive treatment for CRS. Intranasal glucocorticoids are particularly effective in those with coexisting allergic rhinitis (124,125). Daily maintenance therapy with oral or topical decongestants is not considered beneficial for CRS (8); however, use of topical decongestants (oxymetazoline) in combination with nasal steroids may be a useful adjunctive treatment for CRS, and may be safe for up to 4 weeks (126–129).

Treatment of predisposing conditions is more likely to be effective than multiple rounds of increasingly more broad-spectrum antibiotics. If indicated, prolonged treatment (3 to 6 weeks) with antibiotics is thought to be more effective than shorter courses (130). When incomplete resolution of exacerbations occurs, endoscopic or surgically obtained cultures can be helpful to guide antibiotic choices, particularly when broad-spectrum antibiotics such as fluoroquinolones are being considered (92).

When all attempts at pharmacologic management have failed, surgery may be required as adjunctive treatment for chronic or recurrent sinusitis when associated with chronic ostiomeatal obstruction (8). FESS has supplanted older surgical procedures, such as maxillary Caldwell–Luc antrostomy. The basic principle of endoscopic techniques is to resect the inflamed tissues that obstruct the ostiomeatal complex and the anterior ethmoids, and thus directly interfere with normal physiologic drainage (131). Because nasal endoscopic surgery is less invasive, postoperative morbidity has been reduced markedly in comparison with formerly used surgical techniques. Multiple studies have demonstrated short-term improvements in symptoms after surgery for CRS or recurrent

sinusitis (55). A prospective study of 82 patients who underwent endoscopic surgery after failing medical management reported significant initial improvements in self-reported symptoms; however, there was a trend toward recurrence of presenting complaints by 3 years (119). Those patients with AERD were less likely to experience long-term benefits from surgery.

Nonallergic Rhinitis

Symptoms of nonallergic rhinitis are often indistinguishable from those associated with perennial allergic rhinitis. Nonallergic rhinitis is defined as inflammation of the nasal mucosa that is not because of IgE-mediated sensitization. Lack of allergic causation should be proven by the absence of skin test reactivity to a panel of common aeroallergens. A community-based Danish study of over 1,000 adults found that approximately 25% of chronic rhinitis sufferers had nonallergic rhinitis (132). Women were more likely to have nonallergic rhinitis than men, and symptom severity was indistinguishable between allergic and nonallergic rhinitics. Onset after 40 to 50 years of age is more likely with nonallergic versus allergic rhinitis; however, nonallergic rhinitis occurs in children as well (133,134). As many as 40 million Americans have nonallergic rhinitis, or a combination of nonallergic rhinitis and allergic rhinitis (135).

Table 27.1 presents a classification for the nonallergic nasal disorders, which includes the differential diagnosis for conditions that may mimic rhinitis (136).

Evaluation begins with a careful history and nasal examination, preferably with a nasal speculum. Nasal septal deviation is usually obvious. Pale, boggy nasal turbinates characteristic of allergic rhinitis may also be seen in a patient with nonallergic rhinitis with eosinophilia syndrome (NARES) or nasal polyps. The nasal mucosa appears beefy red or hemorrhagic in patients with rhinitis medicamentosa. Cytologic examination of a nasal mucus smear may reveal an abundance of neutrophils, which is suggestive of infectious rhinitis (137). Nasal eosinophils are consistent with allergic rhinitis, NARES, or nasal polyposis (138,139).

Vasomotor rhinitis or idiopathic nonallergic noninfectious rhinitis is the most common of these disorders, excluding viral upper respiratory infections. Symptoms include perennial nasal congestion, rhinorrhea, and postnasal discharge. Ocular symptoms can be present in nonallergic rhinitis, although they tend to be more prominent in allergic rhinitis (140). Typically, nasal symptoms are triggered by irritants in tobacco smoke, chemical fumes, perfumes, or various

scents and noxious odors. Symptoms are classically triggered by rapid changes in temperature. Although the pathophysiology of this condition is not well understood, it has been postulated that environmental factors may trigger neurogenic reflex responses or that symptoms are a consequence of an imbalance in parasympathetic and sympathetic tone (141). Transient receptor potential ion channels on sensory nerve endings on nasal mucosa may act as primary irritant sensors; activation of these channels leads to neuropeptide release with subsequent vasodilation and increase in transudation (142). Gustatory rhinitis is a form of vasomotor rhinitis in which clear rhinorrhea is provoked by eating, particularly when eating hot or spicy foods (143). Other subtypes of vasomotor rhinitis are listed in Table 27.1.

TABLE 27.1 NONALLERGIC NASAL DISORDERS

SUBTYPES OF NONALLERGIC RHINITIS	CONDITIONS THAT MAY MIMIC SYMPTOMS OF RHINITIS
Vasomotor rhinitis	Nasal polyps
Gustatory rhinitis	Structural/mechanical factors
Irritant triggered (e.g., chlorine)	Deviated septum/septal wall anomalies
Cold air	Adenoidal hypertrophy
Exercise (e.g., running)	Trauma
Undetermined or poorly defined triggers	Foreign bodies
Nonallergic rhinitis with eosinophilia syndrome (NARES)	Nasal tumors
Atrophic rhinitis	Benign
Rhinitis medicamentosa (topical vasocontrictors)	Malignant
Drug-induced rhinitis (oral medications)	Choanal atresia
Hormonally induced rhinitis	Cleft palate
Pregnancy rhinitis	Pharyngonasal reflux
Menstrual cycle related	Acromegaly (excess growth hormone)
Infectious rhinitis	Rhinitis associated with inflammatory-immunologic disorders
Acute	Granulomatous infections
Chronic	Granulomatosis with polyangiitis
	(Wegener syndrome)
	Sarcoidosis
	Midline granuloma

	Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)
	Relapsing polychondritis
	Amyloidosis
	Cerebrospinal fluid rhinorrhea
	Ciliary dyskinesia syndrome

NARES is an inflammatory nasal disorder in which eosinophils are detectable on a nasal smear (>5% to >20% nasal eosinophils), but skin tests to relevant aeroallergens are negative (144–146). The cause of this condition is unknown. NARES may be a precursor to the development of nasal polyposis and aspirin intolerance (147).

Primary atrophic rhinitis is a disorder of unknown origin, which is characterized by formation of thick, malodorous, dry crusts that obstruct the nasal cavity (148,149). Secondary atrophic rhinitis is more common in the Western world, and is associated with granulomatous disease, nasal irradiation, trauma, and prior sinonasal surgery. Removal of the middle and/or inferior turbinates in particular may predispose to development of secondary atrophic rhinitis (150).

Rhinitis medicamentosa can result from the chronic use or abuse of topical decongestants, or from cocaine use. Excessive use of topical vasoconstrictor agents, such as neosynephrine or oxymetazoline, can result in epistaxis, "rebound" nasal congestion, and rarely cause nasal septal perforation (151). Intranasal cocaine use can result in the same signs and symptoms. Benzalkonium chloride, a preservative commonly used in over-the-counter and prescription aqueous products, might play a causative role in rhinitis medicamentosa (152).

Drug-induced rhinitis occurs as an adverse effect of certain oral medications (see Table 27.2) (153). In particular, angiotensin-converting enzyme inhibitors have been reported to cause rhinorrhea and vasomotor symptoms in association with chronic cough, which resolve after withdrawal of the drug (154). Other oral medications associated with drug-induced rhinitis include phosphodiesterase type 5 inhibitors (e.g., sildenafil), nonsteroidal anti-inflammatory drugs, certain

psychotropic medications, gabapentin, and α-antagonists used for benign prostatic hypertrophy (153,155).

Nasal congestion and rhinorrhea are common during pregnancy. This may be related to underlying allergic rhinitis, sinusitis, rhinitis medicamentosa, or may be due to vasomotor rhinitis of pregnancy ("pregnancy rhinitis"). "Pregnancy rhinitis" occurs in approximately one-fifth of pregnant women and manifests primarily as nasal congestion that starts before the last 6 weeks of pregnancy and resolves within 2 weeks of delivery (156). It may be due to progesterone or estrogen-induced nasal vasodilation and enhancement of mucus secretion, or possibly to placental growth hormone (157).

TABLE 27.2 CAUSATIVE AGENTS FOR DRUG-INDUCED RHINITIS

Antihypertensives
  Amiloride
  ACE inhibitors[a]
  ARBs[b]
  β-Blockers
  Chlorothiazine
  Clonidine
  Hydralazine
  Hydrochlorothiazide
  Methyldopa
α-Adrenergic antagonists[c]
  Prazosin
  Doxazosin
  Phentolamine
  Terazosin
  Tamsulosin
Phosphodiesterase type 5 inhibitors
  Sildenafil
  Tadalafil
  Verdenafil

Psychotropic agents
  Chlordiazepoxide-amitryptyline
  Chlorpromazine
  Risperidone
  Thioridazine
Ovarian hormonal agents
  Oral contraceptives[d]
  Exogenous estrogens
Pain relievers
  Aspirin
  Nonsteroidal anti-inflammatory drugs
Miscellaneous
  Cocaine[e]
  Gabapentin

[a]Angiotensin-converting enzyme inhibitors.

[b]Angiotensin receptor blockers (177).

[c]Used for hypertension or benign prostatic hypertrophy depending on specific drug.

[d]May not apply to modern oral contraceptives (178).

[e]Mechanism may be similar to other topical vasoconstrictors.

Adapted from Ramey JT, Bailen E, Lockey RF. Rhinitis medicamentosa. *J Investig Allergol Clin Immunol*. 2006;16(3):148–155.

Local allergic rhinitis is caused by local production of sIgE (158). Skin tests and serum sIgE are negative, but sIgE can be measured in nasal lavage and nasal provocation tests are positive. The prevalence of this condition has not been reported.

Conditions that mimic rhinitis must be considered in the differential diagnosis. A grossly deviated nasal septum, nasal tumors, or a foreign body can be the source of unilateral nasal obstruction refractory to medical treatment. Cerebral spinal fluid (CSF) rhinorrhea is characterized by clear nasal discharge. It occurs in 5% of all basilar skull fractures but can be present in patients with no history of trauma. Detection of β-2 transferrin in the CSF is useful in confirming the diagnosis (159,160).

Treatment

Selection of therapy for vasomotor rhinitis is empiric, and there are variable responses to different regimens. Azelastine hydrochloride is a topical antihistamine that has been shown to decrease nasal congestion and postnasal drip associated with vasomotor rhinitis in multiple randomized controlled trials (161–164). Olopatadine hydrochloride nasal spray has shown similar efficacy to azelastine for vasomotor rhinitis (165). Intranasal steroids are beneficial for some cases of vasomotor rhinitis (166,167). The combination of azelastine with intranasal steroids (fluticasone proprionate) provides greater symptom relief than either agent alone (161,168). When not contraindicated by coexisting medical conditions, oral decongestants are often effective for congestion caused by vasomotor rhinitis when given as 12-hour slow-release preparations (e.g., pseudoephedrine) (169). Nasal ipratropium, an anticholinergic agent, is proven to be effective in treating rhinorrhea associated with nonallergic rhinitis, and is the treatment of choice for gustatory and cold air–induced rhinitis (143,170,171). A recent *Cochrane Database Review* of four studies including 302 patients concluded that intranasal capsaicin may be a treatment option for vasomotor rhinitis (172). Environmental triggers, such as tobacco smoke and irritants, encountered at home or work should be avoided.

The syndrome of NARES responds best to intranasal glucocorticoids (167). Atrophic rhinitis is treated chronically with saline irrigation, with topical and systemic antibiotics prescribed for acute infections (150). Patients with rhinitis medicamentosa should discontinue offending medications. Intranasal glucocorticoids may be of considerable benefit in these patients in decreasing mucosal edema (173).

For rhinitis of pregnancy, medication use should be minimized. Saline rinses and mechanical alar dilators may be appropriate. If necessary, nasal steroids (i.e., intranasal budesonide) may be safe and effective for controlling chronic allergic rhinitis symptoms encountered during pregnancy, but do not have proven efficacy for treating pure pregnancy rhinitis (156,174,175). Nasal ipratropium could also be considered to treat associated rhinorrhea (170,176).

Nasal obstruction caused by a severely deviated septum requires septoplasty. Some patients with CSF rhinorrhea recover spontaneously, or with medical treatment alone. When persistent, intravenous antibiotics should be started to prevent meningitis, and endoscopic or open surgery often is required to repair a dural tear (8).

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Allergic Diseases of the Eye and Ear

SEONG H. CHO, SULTAN ALANDIJANI, AND PHIL LIEBERMAN

■ THE EYE

The allergic eye diseases are contact dermatoconjunctivitis, acute allergic conjunctivitis, vernal conjunctivitis, and atopic keratoconjunctivitis (allergic eye diseases associated with atopic dermatitis). Several other conditions mimic allergic disease and should be considered in any patient presenting with conjunctivitis. These include the blepharoconjunctivitis associated with staphylococcal infection, seborrhea and rosacea, acute viral conjunctivitis, chlamydial conjunctivitis, keratoconjunctivitis sicca, herpes simplex keratitis, giant papillary conjunctivitis, vasomotor (perennial chronic) conjunctivitis, and the "floppy eye syndrome." Each of these entities is discussed in relationship to the differential diagnosis of allergic conjunctivitis. The allergic conditions themselves are emphasized.

In addition to the systematic discussion of these diseases, because the chapter is written for the nonophthalmologist, an anatomic sketch of the eye (Fig. 28.1) is included.

Diseases Involving the Eyelids

There are two conditions to be considered when the eyelids are involved. They are contact dermatitis and atopic keratoconjunctivitis.

Contact Dermatitis and Dermatoconjunctivitis

Because the skin of the eyelid is thin (0.55 mm), it is particularly prone to develop both immune and irritant contact dermatitis. When the causative agent has contact with the conjunctiva and the lid, a dermatoconjunctivitis occurs.
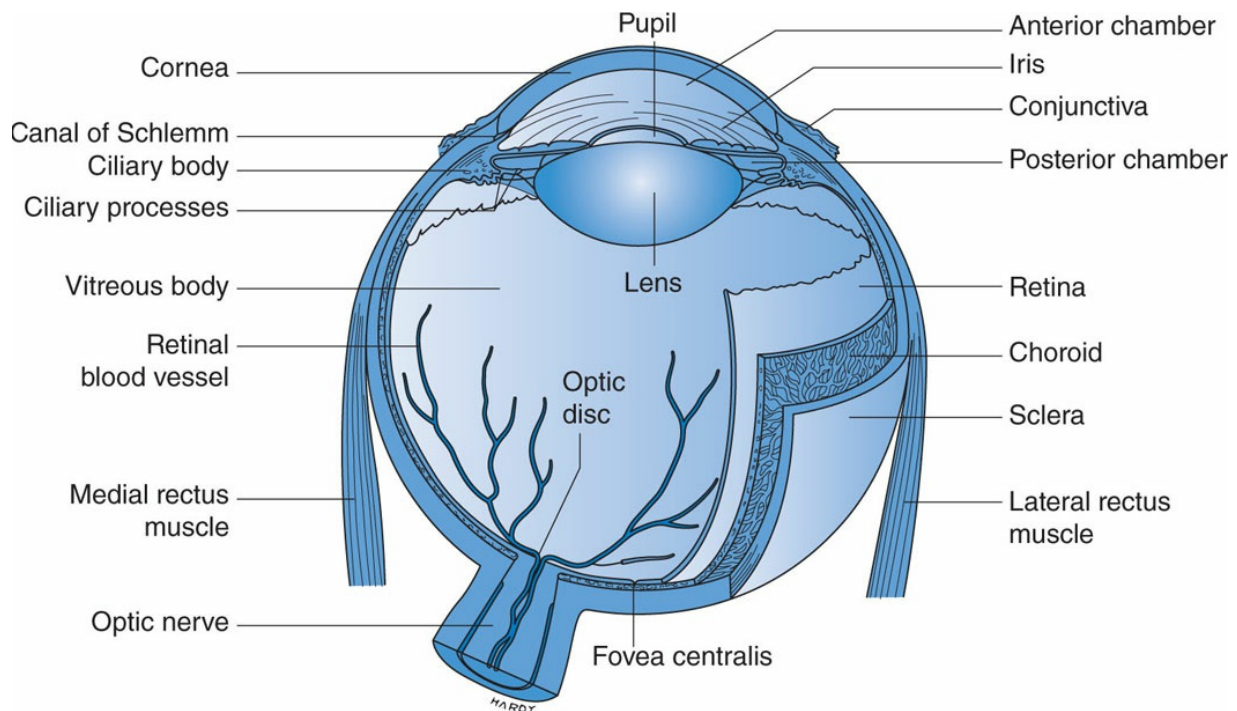
■ **FIGURE 28.1** Transverse section of the eye. (From Brunner L, Suddarth D. *Textbook of Medical-Surgical Nursing.* 4th ed. Philadelphia: JB Lippincott, 1980, with permission.)

Clinical Presentation

Contact dermatitis and dermatoconjunctivitis affect women more commonly than men because women use cosmetics more frequently. Vesiculation may occur early, but by the time the patient seeks care, the lids usually appear thickened, red, and chronically inflamed. Peeling and scaling of the eyelids also occur with chronic exposure. If the conjunctiva is involved, there is erythema and tearing. A papillary response with vasodilation and chemosis occurs. Pruritus is the cardinal symptom; a burning sensation may also be present. Rubbing the eyes intensifies the itching. Tearing can occur. An erythematous blepharitis is common, and in severe cases, keratitis can result.

Causative Agents

Contact dermatitis and dermatoconjunctivitis can be caused by agents directly applied to the lid or conjunctiva, aerosolized or airborne agents contacted by chance, and cosmetics applied to other areas of the body. In fact, eyelid dermatitis occurs frequently because of cosmetics (e.g., nail polish, hair spray) applied to other areas of the body (1). However, agents applied directly to the eye are the most common causes. Contact dermatitis can be caused by eye makeup, including eyebrow pencil and eyebrow brush-on products, eye shadow, eye liner, mascara, artificial lashes, and lash extender. These products contain

coloring agents, lanolin, paraben, sorbitol, paraffin, petrolatum, and other substances such as vehicles and perfumes (1). Brushes and pads used to apply these cosmetics can also produce dermatitis. In addition to agents applied directly only to the eye, soaps and face creams can produce a selective dermatitis of the lid because of the thin skin in this area. Cosmetic formulations are frequently altered (1). Therefore, a cosmetic previously used without ill effect can become a sensitizing agent.

Any medication applied to the eye can produce a contact dermatitis or dermatoconjunctivitis. Ophthalmic preparations contain several sensitizing agents, including benzalkonium chloride, chlorobutanol, chlorhexidine, ethylenediaminetetraacetate acid (EDTA), and phenylmercuric salts. EDTA cross-reacts with ethylenediamine, so that patients sensitive to this agent are subject to develop dermatitis as a result of several other medications. Today, antibiotics, antivirals, and antiglaucoma drugs are probably the major causes of iatrogenic contact dermatoconjunctivitis. Several other topically applied medications, however, have been shown to cause dermatoconjunctivitis. These include antihistamines, such as antazoline, as well as atropine, pilocarpine, phenylephrine, epinephrine, and topical anesthetics.

Of continuing importance is the conjunctivitis associated with the wearing of contact lenses, especially soft lenses. Reactions can occur to the lenses themselves or to the chemicals used to treat them. Both toxic and immune reactions can occur to contact lens solutions. Thimerosal, a preservative used in contact lens solutions, has been shown to produce classic, cell-medicated contact dermatitis (2). Other substances found in lens solutions that might cause either toxic or immune reactions are the bacteriostatic agents (methylparaben, chlorobutanol, and chlorhexidine) and EDTA, which is used to chelate lens deposits. With the increasing use of disposable contact lenses, the incidence of contact allergy to lenses and their cleansing agents appears to be declining.

Dermatitis of the lid and conjunctiva can also result from exposure to airborne agents. Hair spray, volatile substances contacted at work, and the oleoresin moieties of airborne pollens have all been reported to produce contact dermatitis and dermatoconjunctivitis. Hair preparations and nail enamel frequently cause problems around the eye while sparing the scalp and the hands. Finally, *Rhus* dermatitis can affect the eye, producing unilateral periorbital edema, which can be confused with angioedema.

Diagnosis and Identification of Causative Agents

The differential diagnosis includes seborrheic dermatitis and blepharitis,

infectious eczematous dermatitis (especially chronic staphylococcal blepharitis), and rosacea. Seborrheic dermatitis can usually can differentiated from contact dermatitis on the basis of seborrheic lesions elsewhere and the lack or pruritus. Also, pruritus does not occur in staphylococcal blepharitis or rosacea. If the diagnosis is in doubt, an ophthalmology consultation should be obtained.

In some instances, the etiologic agent may be readily apparent. This is usually the case in dermatitis caused by the application of topical medications. However, many cases present as chronic dermatitis, and the cause is not readily apparent. In such instances, an elimination-provocation procedure and patch tests can identify the offending substance. The elimination-provocation procedure requires that the patient stop using all substances under suspicion. This is often difficult because it requires the complete removal of all cosmetics, hair sprays, spray deodorants, and any other topically applied substances. It should also include the cessation of visits to hair stylists and day spas during the course of the elimination procedure. The soaps and shampoo should be changed. A bland soap (e.g., Basis) and shampoo free of formalin (e.g., Neutrogena, Ionil) should be employed. In recalcitrant cases, the detergent used to wash the pillowcases should also be changed. The elimination phase of the procedure should continue until the dermatitis subsides, or for a maximum of 1 month. When the illness has cleared, cosmetics and other substances can be returned at a rate of 1 every week. On occasion, the offending substances can be identified by the recurrence of symptoms upon the reintroduction of the substance in question.

Patch tests can be helpful in establishing a diagnosis (3,4). However, the skin of the lid is markedly different from that of the back and forearm, and drugs repeatedly applied to the conjunctival sac concentrate there, producing high local concentrations of the drug. Thus, false-negative results from patch tests are common (1). Testing should be performed, not only to substances in standard patch test kits but also to the patient's own cosmetics. In addition to the cosmetics themselves, tests can be performed to applying agents, such as sponges and brushes. Both open- and closed-patch tests are indicated when testing with cosmetics (1). Fisher (4) describes a simple test consisting of rubbing the substances into the forearm three times daily for 4 to 5 days and then examining the sites. Because of the difficulty involved in establishing the etiologic agent with standard patch test kits, an ophthalmic patch test tray (Table 28.1) has been suggested (3).

Therapy

The treatment of choice is removal of the offending agent. On occasion, this can

be easily accomplished. An example of this is the switch from chemically preserved to heat-sterilized systems in patients with contact lens-associated contact conjunctivitis. The offending agent, however, frequently cannot be identified, regardless of the diagnostic procedures applied. In these instances, chronic symptomatic therapy, possibly in conjunction with an ophthalmologist, is all that can be offered to the patient.

Symptomatic relief can be obtained with topical corticosteroid creams, ointments, and drops. Corticosteroid drops should be employed only under the direction of the ophthalmologist. Cool tap-water soaks and boric acid eye baths may help.

Atopic Dermatitis Ocular Involvement

Manifestations of atopic involvement of the eyelids are similar to immune and irritant contact dermatitis of the lids. Chronic scaling, pruritus, and lichenification of the lids are most commonly due to these two disorders, and both should be considered in the differential diagnosis. The features that distinguish atopic dermatitis of the lid from contact and irritant dermatitis are the following:

- The presence of atopic dermatitis manifestations elsewhere and concomitant existence of allergic respiratory disease.

- Pruritus is usually more common and intense in atopic dermatitis.

- Madarosis (lash loss) and trichiasis (lash misdirection) are more common in atopic dermatitis.

- Involvement of the eye itself is also present in most cases of atopic dermatitis of the lid.

- The ocular findings are conjunctival erythema and swelling, limbal papillae, keratoconus (see below), anterior and posterior subcapsular cataracts, and occasionally corneal erosion with ulcers, neovascularization, and scarring.

- A family history of atopic disease is usually noted.

Dermatitis infecting the lids can present with a myriad of manifestations. The hallmark is intense bilateral itching and burning of the lids with scaling. There is often accompanying tearing and photophobia. Like vernal conjunctivitis, patients with ocular manifestations as well can exhibit a thick, ropy discharge.

The lids are edematous, scaly, and thickened. There is a wrinkled appearance of the skin. Lichenification occurs with chronic involvement. Eyelid

malpositions are common.

Because of the chronic itching, the patient's rubbing and scratching of their lids leads to further changes such as fissures, which occur commonly near the lateral canthus (5).

Periorbital features of allergic disease have also been described. The classic "Dennie–Morgan" fold is a crease extending from the inner canthus laterally to the mid-pupillary line of the lower lid. There is often periorbital darkening referred to as "the allergic shiner." The lateral eyebrows are often absent (Hertoghe sign). Eyelid margin (blepharitis) involvement is characteristic. The findings resemble those of chronic bacterial blepharitis (see below), and indeed these findings may be because of bacterial overgrowth occurring with atopy. There is hyperemia and an exudate with crusting in the morning.

TABLE 28.1 SUGGESTED OPHTHALMIC TRAY FOR PATCH TESTING

COMPOUND	PATCH TEST CONCENTRATION (%)	VEHICLE
Preservatives		
Benzalkonium chloride	0.1	aq
Benzethonium chloride	1	aq
Chlorhexidine gluconate	1	aq
Cetalkonium chloride	0.1	aq
Sodium EDTA	1	aq
Sorbic acid	2.5	pet
Thimerosal	0.1; 1	pet

β-Adrenergic Blocking Agents		
Befunolol	1	aq
Levobunolol HCI	1	aq
Metipranolol	2	aq
Metoprolol	3	aq
Timolol	0.5	aq
Mydriatics		
Atropine sulfate	1	aq
Epinephrine HCI	1	aq
Phenylephrine HCI	10	aq
Scopolamine hydrobromide	0.25	aq
Antibiotics		
Bacitracin	5	pet
Chloramphenicol	5	pet
Gentamicin sulfate	20	pet
Kanamycin	10	pet

Neomycin sulfate	20	pet
Polymyxin B sulfate	20	pet

Antiviral Drugs

Idoxuridine	1	pet
Trifluridine	5	pet

Antihistamines or Antiallergic Drug

Chlorpheniramine maleate	5	pet
Sodium cromoglycate	2	aq

Anesthetics

Benzocaine	5	pet
Procaine	5	aq
Oxybuprocaine	0.5	aq
Proxymetacaine	0.5	aq

Enzymatic Cleaners

Papain	1	pet

Tegobetaine	1	aq

Miotics		
Pilocarpine	1	aq
Tolazoline	10	aq
Echothiophate iodide	1	aq

Other		
Epsilon aminocaproic acid	1	aq

aq, aqueous; EDTA, ethylenediaminetetraacetic acid; pet, petrolatum.

From Mondino B, Salamon S, Zaidman G. Allergic and toxic reactions in soft contact lens weavers. *Surv Ophthalmol*. 1982;26:337–344, with permission.

Owing to misdirection of the lashes, there is often contact of the lash with the conjunctivae, and this can be particularly bothersome to patients.

As noted, bacterial colonization is not uncommon. *Staphylococcal aureus* is probably the most common organism involved. Presumably, *Staphylococcus* colonizes the eye through contact with the hands. The phenotype of the *Staphylococcus* growing in the eye correlates with that of overgrowth on the skin in the majority of instances (6).

Therapy

Therapy of the lids in atopic dermatitis is similar to that of allergic disease in general. Known environmental exacerbants should, of course, be avoided. Cool compresses and bland moisturizers are helpful. Vaseline and Aquaphor (Beiersdorf, Norwalk, Connecticut) are examples in this regard. Periodic exacerbations of lid inflammation can be treated with low-dose topical corticosteroid ointments. An example is fluorometholone 0.1% ophthalmic ointment. Care must be taken, however, because long-term administration can thin the skin of the eyelid and produce permanent cosmetic changes because

vessels begin to show through the thin skin. The lowest dose for the shortest period of time should be employed.

Tacrolimus and pimecrolimus topical preparation can also be helpful as in atopic dermatitis in general.

Pathophysiology

The pathogenesis of eye involvement in atopic dermatitis, like the pathophysiology underlying abnormalities in the skin, is complex. It certainly involves immunoglobulin E (IgE)-mediated mechanisms, but clearly other inflammatory pathways are also active. Patients with atopic keratoconjunctivitis have elevated tear levels of interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin 2 (IL-2), IL-4, IL-5, and IL-10, thus indicating a combined T_H1 and T_H2 response (7).

However, at least in animal models, there is a clear predominance of the T_H2 phenotype in terms of T cells. The characteristic ocular eosinophilia appears to be dependent upon the presence of this T-cell population (8).

The active role of T cells in allergic disorders of the eye clearly explain the beneficial effect of cyclosporin in these diseases (9).

Acute Allergic Conjunctivitis

Pathophysiology

Acute allergic conjunctivitis is the most common form of allergic eye disease (10). Seasonal allergic conjunctivitis and perennial allergic conjunctivitis are estimated to affect 15% to 45% of the US population (10). Seasonal and perennial allergic conjunctivitis represent 25% to 95% of the total cases of ocular allergy (10,11). And, the incidence of this condition is probably underestimated because the percentage of undiagnosed allergic conjunctivitis in patients presenting with rhinitis may range from 25% to 60% (12). Allergic conjunctivitis is produced by IgE-induced mast cell and basophil degranulation (11,13). As a result of this reaction, histamine, kinins, leukotrienes, prostaglandins, interleukins, chemokines, IL-4, IL-5, and eosinophilic cationic protein, eotaxin, and other mediators are released in the eye (14–17). Patients with allergic conjunctivitis have elevated amounts of total IgE in their tears (18–20), and tear fluid also contains IgE specific for seasonal allergens (21). Eosinophils are found in ocular scrapings (22–24). These eosinophils are activated, releasing contents such as eosinophil cationic protein from their granules. These contents appear in tear fluid as well (24). Ocular challenge with pollen produces both an early- and

a late-phase ocular response (25). In humans, the early phase begins within 20 minutes after challenge. The late phase is dose dependent, and large doses of allergen cause the initial inflammation to persist and progress (25). The late phase differs from that which occurs in the nose and lungs in that it is often continuous and progressive rather than biphasic (25). It is characterized by the infiltration of inflammatory cells, including neutrophils, eosinophils, and lymphocytes. The eosinophil is the predominant cell (25). In addition, during the late-phase reaction, mediators are continually released, including histamine, leukotrienes, and eosinophil contents (26).

Subjects with allergic conjunctivitis demonstrate a typical T_H2 (allergic) profile of cytokines in their tear fluid showing excess production of IL-4 and IL-5 (27–29). If the illness becomes chronic, however, there may be a shift in cytokine profile to a T_H1 pattern with excess production of IFN-γ, as seen in atopic keratoconjunctivitis (29,30).

Subjects with allergic conjunctivitis have an increased number of mast cells in their conjunctivae (31), and mast cell numbers increase during the allergy season. In addition, the phenotype is modified as mucosal mast cells increase to a greater degree than connective tissue mast cell (11). Patients with allergic conjunctivitis are hyperresponsive to intraocular histamine challenge (32). Of interest is the fact that there is evidence of complement activation. Elevated levels of C3a des-Arg appear in tear fluid (28). The consequences of this immune reaction are conjunctival vasodilation and edema. The clinical reproducibility of the reaction is dependable. Instillation of allergen into the conjunctival sac was once used as a diagnostic test (33).

Clinical Presentation

Acute allergic conjunctivitis is usually recognized easily. Intense itching is the dominant feature (34). Rubbing the eyes intensifies the symptoms. The illness is almost always bilateral. However, unilateral acute allergic conjunctivitis can occur secondary to manual contamination of the conjunctiva with allergens, such as foods and animal dander. Ocular signs are usually minimal despite significant symptoms. The conjunctiva may be injected and edematous. In severe cases, the eye may be swollen shut. These symptoms of allergic conjunctivitis may be so severe as to interfere with the patient's sleep and work.

Allergic conjunctivitis rarely occurs without accompanying allergic rhinitis. Nevertheless, the eye symptoms may be more prominent than nasal symptoms and can be the patient's major complaint. However, if symptoms or signs of

allergic rhinitis are totally absent, the diagnosis of allergic conjunctivitis is doubtful. Allergic conjunctivitis also exists in a chronic, perennial form. Symptoms are usually less intense. As in acute allergic conjunctivitis, ocular findings on physical examination may not be impressive.

Diagnosis and Treatment

The diagnosis of allergic conjunctivitis can usually be made on the basis of history. Usually, there is an atopic personal or a family history; the disease is usually seasonal. At times, the patient may be able to define the offending allergen accurately. Skin tests are confirmatory. Stain of the conjunctival secretions may show numerous eosinophils, but the absence of eosinophils does not exclude the condition (35). Normal individuals do not have eosinophils in conjunctival scrapings; therefore, the presence of one eosinophil is consistent with the diagnosis (35). The differential diagnosis should include other forms of acute conjunctivitis, including viral and bacterial conjunctivitis, contact dermatoconjunctivitis, conjunctivitis sicca, and vernal conjunctivitis.

Treating allergic conjunctivitis is the same as for other atopic illness: avoidance, symptomatic relief, and immunotherapy, in that order. When allergic conjunctivitis is associated with respiratory allergic disease, the course of treatment is usually dictated by the more debilitating respiratory disorder. Avoiding ubiquitous aeroallergens is impractical, but avoidance measures outlined elsewhere in this text can be employed in the treatment of allergic conjunctivitis.

Effective symptomatic therapy for allergic conjunctivitis can usually be achieved with topical medications. The most significant change in the management of allergic eye disorders since the last edition of this text is the release of new topical agents to treat these disorders. Six classes of topical agents are now available: vasoconstrictors, "classic" antihistamines, "classic" mast cell stabilizers, new agents with multiple "antiallergic" activities, nonsteroidal anti-inflammatory agents, and corticosteroids. Selected examples of these agents are noted in Table 28.2. Corticosteroids are not discussed here because, as a result of their well-known side effects, patients should use them only when prescribed by the ophthalmologist.

TABLE 28.2 REPRESENTATIVE TOPICAL AGENTS USED TO TREAT ALLERGIC EYE DISORDERS

REPRESENTATIVE

DRUG CLASS	TRADE NAME EXAMPLES	DOSAGE	COMMENTS
Vasoconstrictors			
Tetrahydrozoline, phenylephrine, oxymetazoline, naphazoline	Naphcon, Vasocon, Visine	1–2 drops every 4 h prn (not more than qid)	Only helpful for eye redness. Does not relieve itch. Available without prescription. Some concern about "rebound." Contraindicated in narrow-angle glaucoma.
Antihistamines			
Levocabastine	Livostin	1 drop qid	Effective for itching. Available by prescription only. May be more potent than antihistamines available without prescription.
Emedastine	Emadine	1 drop qid	
Combination Vasoconstrictor Plus Antihistamine			
Antazoline, naphazoline	Vasocon-A	1 drop qid	Effective for eye redness and itch. Available without prescription.
Mast Cell Stabilizers			
Lodoxadine	Alomide	1 drop qid	Best when initiated before onset of symptoms.
Cromolyn	Crolom, Opticrom	1 drop qid	

Nedocromil	Allocril	1 drop qid	
Pemirolast	Alamast	1 drop qid	

Nonsteroidal Anti-inflammatory Drugs

Ketorolac	Acular	1 drop qid	Indicated for itching

Drugs with Multiple "Antiallergic" Activities Such as Antihistamine, Mast Cell Stabilizing, and Antieosinophil Effects

Olopatadine preparations	Patanol (0.1%)	1 drop bid	Prescription required
	Pataday (0.2%)	1 drops qd	Prescription required
	Pazeo (0.7%)	1 drop qd	Prescription required
Ketotifen	Zaditor	1 drop every 12 h	Available without prescription
Epinastine	Elestat	1 drop every 12 h	Prescription required
Azelastine	Optivar	1 drop every 12 h	Prescription required
Acaftadine	Lastacraft	1 drop qd	Prescription required
Bepotastine	Bepreve	1 drop qd	Prescription required

bid, two times a day; prn, as needed; qd, once a day; qid, four times a day.

Several preparations contain a mixture of a vasoconstrictor combined with an antihistamine (Table 28.2). These drugs can be purchased over the counter. The antihistamine is most useful not only for itching but also reduces vasodilation. Vasoconstrictors only diminish vasodilation and have little effect on pruritus. They have relatively short duration of action, are subject to tachyphylaxis (36), and can cause rebound vasodilatation. Three frequently employed decongestants are naphazoline, oxymetazoline, and phenylephrine. The two most common antihistamines available in combination products are antazoline and pheniramine maleate.

Levocabastine (Livostin) is an H_1 antihistamine available only by prescription. Levocabastine was specifically designed for topical application. In animal studies, it is 1,500 times more potent than chlorpheniramine on a molar basis (37). It has a rapid onset of action (37), is effective in blocking intraocular allergen challenge (38), and appears to be as effective as other agents, including sodium cromoglycate (39,40) and provides excellent compliance (41).

Emedastine (Emadine) is also a high-potency selective H_1 antagonist with a receptor-binding affinity even higher than levocabastine (42). It has rapid onset of action (within 10 minutes) and a duration of activity of 4 hours (42).

As a rule, vasoconstrictors and antihistamines are well tolerated. However, antihistamines may be sensitizing. In addition, each preparation contains several different vehicles that may produce transient irritation or sensitization. Just as vasoconstrictors in the nose can cause rhinitis medicamentosa, frequent use of vasoconstrictors in the eye results in conjunctivitis medicamentosa. As a rule, however, these drugs are effective and well tolerated (43).

Four mast cell stabilizers are available for therapy, namely, cromolyn sodium, nedocromil sodium, lodoxamide, and pemirolast. All are efficacious and usually well tolerated (44–48). They are more effective when started before the onset of symptoms and used regularly four times a day (46), but they can relieve symptoms if given shortly before ocular allergen challenge (47). Thus, they are also useful in preventing symptoms caused by isolated allergen challenge such as occurs when visiting a home with a pet or mowing the lawn. In these instances, they should be administered immediately before exposure.

Ketorolac tromethamine (Acular) is a nonsteroidal anti-inflammatory agent that is most effective in controlling itching but also ameliorates other symptoms (49). Its effect results from its ability to inhibit the formation of prostaglandins, especially prostaglandin E_2 which causes itching when applied to the conjunctiva (50).

Four agents for the treatment of allergic eye disorders have broad-based antiallergic or anti-inflammatory effects in addition to their antihistamine activity, such as azelastine (Optivar), olopatadine (Patanol and Pataday), ketotifen (Zaditor), and epinastine (Elestat). They prevent mast cell degranulation, reduce eosinophil activity, and downregulate the expression of adhesion molecules as well as inhibit the binding of histamine to the H_1 receptor (51–54). Because of the efficacy and low incidence of side effects, these agents have become the most frequently prescribed class of drugs to treat allergic

conjunctivitis.

Allergen immunotherapy can be helpful in treating allergic conjunctivitis. Subcutaneous immunotherapy (SCIT) for allergic rhinitis demonstrated improvement in ocular allergy symptoms (55). SCIT has been demonstrated to reduce the sensitivity to ocular challenge with grass pollen (56). Sublingual immunotherapy reduces ocular symptoms as well (57).

Vernal Conjunctivitis

Clinical Presentation

Vernal conjunctivitis is a chronic, bilateral, catarrhal inflammation of the conjunctiva most commonly arising in children during the spring and summer. It can be perennial in severely affected patients. It is characterized by an intense itching, burning, and photophobia.

The illness is usually seen during the preadolescent years and often resolves at puberty. Male patients are affected about three times more often than female patients when the onset precedes adolescence, but when there is a later onset, female patients predominate. In the later onset variety, the symptoms are usually less severe. The incidence is increased in warmer climates. It is most commonly seen in the Middle East and along the Mediterranean Sea.

Vernal conjunctivitis presents in palpebral and limbal forms. In the palpebral variety, which is more common, the tarsal conjunctiva of the upper lid is deformed by thickened, gelatinous vegetations produced by marked papillary hypertrophy. This hypertrophy imparts a cobblestone appearance to the conjunctiva, which results from intense proliferation of collagen and ground substance along with a cellular infiltrate (57). The papillae are easily seen when the upper lid is everted. In severe cases, the lower palpebral conjunctiva may be similarly involved. In the limbal form, a similar gelatinous cobblestone appearance occurs at the corneal–scleral junction. Trantas' dots—small, white dots composed mainly of eosinophils—are often present. Usually, there is a thick, stringy exudate full of eosinophils. This thick, ropy, white or yellow mucous discharge has highly elastic properties and produces a foreign body sensation. It is usually easily distinguished from the globular mucus seen in seasonal allergic conjunctivitis or the crusting of infectious conjunctivitis. The patient may be particularly troubled by this discharge, which can string out for more than 2.5 cm (1 inch) when it is removed from the eye. Widespread punctate keratitis may be present. Severe cases can result in epithelial ulceration with scar formation.

Pathophysiology and Cause

The cause of and pathophysiologic mechanisms underlying vernal conjunctivitis remain obscure (58–76). Several features of the disease, however, suggest that the atopic state is related to its pathogenesis. The seasonal occurrence, the presence of eosinophils, and the fact that most of the patients have other atopic disease (58) are circumstantial evidence supporting this hypothesis. In addition, several different immunologic and histologic findings are consistent with an allergic etiology. Patients with vernal conjunctivitis have elevated levels of total IgE (61), allergen-specific IgE (61), histamine (60,62), and tryptase (62) in the tear film. In addition, histologic studies support an immune origin. Patients with vernal conjunctivitis have markedly increased numbers of eosinophils, basophils, mast cells, and plasma cells in biopsy specimens taken from the conjunctiva (62). The mast cells are often totally degranulated (62). Elevated levels of major basic protein are found in biopsy specimens of the conjunctiva (64). Also, in keeping with the postulated role of IgE-mediated hypersensitivity is the pattern of cytokine secretion and T cells found in tears and on biopsy specimens. A T_H2 cytokine profile with increased levels of IL-4 and IL-5 has been found (70). In addition, in animal models, a clear role for T-helper cells type 2 (but not type 1) has been demonstrated. It has been shown that T_H2 cells play a critical role in inducing conjunctival eosinophilic infiltration in this regard. Finally, ocular shields, designed to prevent pollen exposure, have been reported to be therapeutically effective (68).

A role for cell-mediated immunity has also been proposed and is supported by the findings of increased CD4$^+$/CD29$^+$ helper T cells in tears during acute phases of the illness (65). Also, in keeping with this hypothesis is the improvement demonstrated during therapy with topical cyclosporine (66,67).

Fibroblasts appear to be operative in the pathogenesis as well. They may be activated by T-cell or mast cell products. When stimulated with histamine, fibroblasts from patients with vernal conjunctivitis produce excessive amounts of procollagen I and II (69). In addition, they appear to manufacture constitutively increased amounts of transforming growth factor-β, IL-1, IL-6, and TNF-α *in vitro*. The increased levels of cytokines noted *in vitro* are accompanied by increased serum levels of IL-1 and TNF-α as well (70). This overexpression of mediators both locally and systemically probably accounts for the upregulation of adhesion molecules (71) on corneal epithelium noted in this disorder.

Also of interest is the hypothesis that complement, perhaps activated by IgG–allergen immune complexes, plays a role in producing vernal conjunctivitis.

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Pollen-specific IgG antibodies (72) and complement activation products (C3 des-Arg) occur in tears of patients with vernal conjunctivitis (73). The specific IgG antipollen found in the tear film may not be acting through the complement system; however, because much of it appears to be IgG_4 (72), a non-complement-fixing subclass with putative reaginic activity. Also, patients with vernal conjunctivitis have decreased tear lactoferrin, an inhibitor of the complement system (76).

The eosinophilic cellular infiltrate in vernal conjunctivitis may contribute to corneal complications. Eosinophils secrete gelatinase B and polycationic toxic proteins, such as major basic protein and eosinophilic cationic protein. *In vitro* these can cause epithelial damage with desquamation and cellular separation (64).

Enzymatic activity may also play a role in pathophysiology of vernal conjunctivitis. Elevated levels of urokinase and metalloproteinases have been seen in vernal conjunctivitis (74).

Vasomotor complications can occur in this disorder and perhaps produce a hyperreactivity of the conjunctivae. Increased expression of muscarinic and adrenergic receptors and neural transmitters have been shown to occur in vernal conjunctivitis. These abnormalities could possibly result in hypersecretion and corneal hyperreactivity (75).

Diagnosis and Treatment

Vernal conjunctivitis must be distinguished from other conjunctival diseases that present with pruritus or follicular hypertrophy. These include acute allergic conjunctivitis, conjunctivitis and keratoconjunctivitis associated with atopic dermatitis, the giant papillary conjunctivitis associated with soft contact lenses and other foreign bodies, the follicular conjunctivitis of viral infections, and trachoma (rarely found in the United States).

In most instances, the distinction between acute allergic conjunctivitis and vernal conjunctivitis is not difficult. However, in the early phases of vernal conjunctivitis or in mild vernal conjunctivitis, giant papillae may be absent. In such instances, the distinction may be more difficult because both conditions occur in atopic individuals, and pruritus is a hallmark of each. However, in vernal conjunctivitis, the pruritus is more intense, the tear film contains a significantly greater concentration of histamine and greater amounts of eosinophils, and the conjunctival epithelium has more abundant mast cells (63). Also, the cornea is not involved in acute allergic conjunctivitis.

The conjunctivitis and keratoconjunctivitis associated with atopic dermatitis can be similar to vernal conjunctivitis. In atopic dermatitis, the conjunctivitis can produce hypertrophy and opacity of the tarsal conjunctiva (77). A form of keratoconjunctivitis with papillary hypertrophy and punctate keratitis can occur (78,79). Many of these patients have signs and symptoms typical of vernal conjunctivitis, including giant follicles and pruritus. In addition, vernal conjunctivitis and atopic dermatitis can occur together in the same patient. However, because the treatment of both conditions is similar, the distinction, except for its prognostic value, may not be essential.

The giant papillary conjunctivitis caused by wearing of soft contact lenses is similar to that of vernal conjunctivitis. Patients complain of itching, mucous discharge, and a decreasing tolerance to the lens. Symptoms usually begin 3 to 36 months after lenses are prescribed (80). The syndrome can occur with hard and soft lenses and can be seen with exposed sutures (80) and plastic prostheses (81). Thus, chronic trauma to the lid appears to be the common inciting agent. Several features distinguish this entity from vernal conjunctivitis. Lens-associated papillary conjunctivitis causes less intense itching and shows no seasonal variation. It resolves with discontinuation of lens use.

Viral infections can be distinguished from vernal conjunctivitis by their frequent association with systemic symptoms and the absence of pruritus. A slit-lamp examination can produce a definitive distinction between these two entities.

Patients with mild vernal conjunctivitis can be treated with cold compresses and topical vasoconstrictor-antihistamine preparations. Levocabastine has been shown to be effective in a double-blind, placebo-controlled trial of 46 patients over a period of 4 weeks (82). Oral antihistamines may be of modest help. Cromolyn sodium and lodoxamide have been used effectively not only for milder but also for more recalcitrant, chronic forms of the condition (83–87). Cromolyn has been shown to decrease conjunctival injection, punctate keratitis, itching, limbal edema, and tearing when administered regularly. It may be more effective in patients who are atopic (85). In a multicenter, double-blind 28-day study, another mast cell stabilizer, lodoxamide, was found to be more effective than cromolyn sodium (87).

Aspirin (88,89) has been found to be helpful in a dose of 0.5 to 1.5 g daily. Ketorolac tromethamine has not been approved for use in vernal conjunctivitis, but based on the studies of aspirin, it might be an effective agent in this regard. Acetylcysteine 10% (Mucomyst) has been suggested as a means of counteracting

viscous secretions. In severe cases, cyclosporine has been used (90).

None of the above medications is universally effective, however, and topical corticosteroids often are necessary. If topical corticosteroids are needed, the patient should be under the care of an ophthalmologist. Fortunately, spontaneous remission usually occurs at puberty.

Perhaps a more appropriate name for this disorder would be vernal keratoconjunctivitis because corneal involvement is common and can be severe. Corneal complications are as a result of uncontrolled inflammation and can be site threatening (91).

Other Eye Manifestations Associated with Atopic Dermatitis

Atopic dermatitis is associated with several manifestations of eye disease (92–98). These include lid dermatitis, blepharitis, conjunctivitis, keratoconjunctivitis, keratoconus, cataracts, and a predisposition to develop ocular infections, especially with herpes simplex and vaccinia viruses (92). Lid involvement has been discussed in detail previously.

Atopic dermatitis patients with ocular complications can be distinguished from those without ocular disease in that they have higher levels of serum IgE and more frequently demonstrate IgE specific to rice and wheat. Those with associated cataract formation have the highest levels of IgE. Patients with ocular complications also have increased tear histamine and leukotriene B4 levels compared with atopic dermatitis subjects without ocular complications (93).

As with other allergic eye conditions, subjects with atopic keratoconjunctivitis have cells in ocular tissue that exhibit a T_H2 cytokine profile with increased expression of messenger RNA for IL-4 and IL-5. Subjects with allergic keratoconjunctivitis, however, are different from those with vernal conjunctivitis in that they also express increased levels of IFN-γ and IL-2, indicating that in later stages of this disease, an element of delayed hypersensitivity is involved in the pathogenesis. Lid involvement can resemble contact dermatitis. The lids become thickened, edematous, and coarse; the pruritus may be intense.

Conjunctivitis may vary in intensity with the degree of skin involvement of the face (76). It resembles acute allergic conjunctivitis and to some extent resembles vernal conjunctivitis. It actually may be allergic conjunctivitis occurring with atopic dermatitis.

Atopic keratoconjunctivitis usually does not appear until the late teenage

years. The peak incidence is between 30 and 50 years of age. Male patients are affected in greater numbers than female patients.

Atopic keratoconjunctivitis is bilateral. The major symptoms are itching, tearing, and burning. The eyelids may be red, thickened, and macerated. There is usually erythema of the lid margin and crusting around the eyelashes. The palpebral conjunctiva may show papillary hypertrophy. The lower lid is usually more severely afflicted and more often involved. Punctate keratitis can occur, and the bulbar conjunctiva is chemotic.

Atopic keratoconjunctivitis must be differentiated from chronic blepharitis of nonallergic origin and vernal conjunctivitis. This may be difficult in the case of blepharitis. Indeed, staphylococcal blepharitis often complicates this disorder. Vernal conjunctivitis is usually distinguished from atopic keratoconjunctivitis by the fact that it most often involves the upper rather than lower lids and is more seasonal. It also occurs in a younger age group. The papillae in vernal conjunctivitis are larger. Cromolyn sodium is helpful in treating atopic keratoconjunctivitis (95). Topical corticosteroids often are needed, however. Their use should be under the direction of the ophthalmologist.

Keratoconus occurs less frequently than conjunctival involvement. The cause of the association between atopic dermatitis and keratoconus is unknown, but there appears to be no human leukocyte antigen haplotype that distinguishes atopic dermatitis patients with keratoconjunctivitis from patients without it or from controls (77).

The incidence rate of cataract formation in atopic dermatitis has been reported to range from 0.4% to 25% (77). These cataracts may be anterior or posterior in location, as opposed to those caused by administering corticosteroids, which are usually posterior. They have been observed in both children and adults. They may be unilateral or bilateral. Their presence cannot be correlated with the age of onset of the disease, its severity, or its duration (96). The pathophysiology involved in the formation of cataracts is unknown, but patients with atopic cataracts have higher serum IgE levels (96) and have elevated levels of major basic protein in aqueous fluid and the anterior capsule, which is not found in senile cataracts (97).

Eyelid disorders may be the most common ocular complaint in patients with atopic dermatitis (98). Dermatitis of the lid produces itching with lid inversion. The skin becomes scaly, and the skin of the eyes around the lid may become more wrinkled. The skin is extremely dry. The lesion is pruritic, and the disorder can be confused with contact dermatitis of the lid.

Herpes keratitis is more common in patients with atopic dermatitis. This condition may be recurrent, and recalcitrant epithelial defects can occur (98).

As with vernal keratoconjunctivitis, atopic keratoconjunctivitis can be site threatening (99).

Blepharoconjunctivitis (Marginal Blepharitis)

Blepharoconjunctivitis (marginal blepharitis) refers to any condition in which inflammation of the lid margin is a prominent feature of the disease. Conjunctivitis usually occurs in conjunction with the blepharitis. Three illnesses are commonly considered under the generic heading of blepharoconjunctivitis: bacterial (usually staphylococcal) blepharoconjunctivitis, seborrheic blepharoconjunctivitis, and rosacea. They often occur together. Blepharoconjunctivitis accounts for 4.5% of all ophthalmologic problems presenting to the primary care physician (100).

Staphylococcal Blepharoconjunctivitis

The staphylococcal organism is probably the most common cause of conjunctivitis and blepharoconjunctivitis. The acute bacterial conjunctivitis is characterized by irritation, redness, and mucopurulent discharge with matting of the eyelids. Frequently, the conjunctivitis is present in a person with low-grade inflammation of the eyelid margins.

In the chronic form, symptoms of staphylococcal blepharoconjunctivitis include erythema of the lid margins, matting of the eyelids on awakening, and discomfort, which is usually worse in the morning. Examination frequently shows yellow crusting of the margin of the eyelids, with collarette formation at the base of the cilia, and disorganized or missing cilia. If the exudates are removed, ulceration of the lid margin may be visible. Fluorescein staining of the cornea may show small areas of dye uptake in the inferior portion. It is believed that exotoxin elaborated by *Staphylococcus* organisms is responsible for the symptoms and signs. Because of the chronicity of the disease and the subtle findings, the entity of chronic blepharoconjunctivitis of staphylococcal origin can be confused with contact dermatitis of the eyelids and contact dermatoconjunctivitis. The absence of pruritus is the most important feature distinguishing staphylococcal from contact dermatoconjunctivitis.

Seborrheic Dermatitis of the Lids

Staphylococcal blepharitis can also be confused with seborrheic blepharitis. Seborrheic blepharitis occurs as part of seborrheic dermatitis. It is associated

with oily skin, seborrhea of the brows, and usually scalp involvement. The scales, which occur at the base of the cilia, tend to be greasy, and if these are removed, no ulceration is seen. There is no pruritus.

Rosacea

Rosacea involving the eyes can be severe even if the skin involvement is minor. Patients present with an angry, erythematous chronic conjunctivitis. The eyelid margin is involved with erythema and meibonium gland dysfunction. The glands are dilated, and their orifices plugged. The pressure on the eyelids below the gland openings will often produce a toothpaste-like secretion. Chronic inflammation can result in loss of secretion and conjunctivitis sicca. Complications include hordeola, chalazia, and telangiectasia. Of course, there are cutaneous manifestations of telangiectasia with flushing as well.

The blepharitis is manifested by collarettes, loss of lashes, discoloration, and whitening and misdirection of the lashes. There is usually marked erythema of the lid margin. Vessels that are telangiectasia can be seen crossing the eyelid margin.

Patients often present with these manifestations thinking they are allergy related, and therefore, this condition must always be kept in mind when making a differential diagnosis. It is important to be aware of the disorder because it can result in corneal erosions with neovascularization, and there can be an associated episcleritis and iritis.

Diagnosis and Treatment of Blepharoconjunctivitis

In all three forms of blepharoconjunctivitis, the cardinal symptoms are burning, redness, and irritation. True pruritus is usually absent or minimal. The inflammation of the lid margin is prominent. The discharge is usually mucopurulent, and matting in the early morning may be an annoying feature. In the seborrheic and rosacea forms, cutaneous involvement elsewhere is present.

All three forms are usually chronic and are often difficult to manage. In staphylococcal blepharoconjunctivitis, lid scrubs using a cotton-tipped applicator soaked with baby shampoo and followed by the application of a steroid ointment may be helpful. Commercially available lid scrubs specifically designed to treat this condition are also available. Control of other areas of seborrhea is necessary. Tetracycline or doxycycline can be beneficial in the therapy of rosacea. Ophthalmologic and dermatologic consultation may be needed.

Infectious Conjunctivitis/Keratitis

Viral Conjunctivitis

Viral conjunctivitis is the most common cause of red eye. It has several characteristics that distinguish it from allergic and bacterial disease. They include:

- Profuse watery discharge without purulence.

- Usually occurs during an upper respiratory tract infection (latter stages).

- May have palpable preauricular node.

- There is no itching.

Viral conjunctivitis is usually of abrupt onset, frequently beginning unilaterally and involving the second eye within a few days. Conjunctival injection, slight chemosis, watery discharge, and enlargement of a preauricular lymph node help to distinguish viral infection from other entities. Clinically, lymphoid follicles appear on the conjunctiva as elevated avascular areas, which are usually grayish. These correspond to the histologic picture of lymphoid germinal centers. Viral conjunctivitis is usually of adenoviral origin and is frequently associated with a pharyngitis and low-grade fever in pharyngoconjunctival fever.

Epidemic keratoconjunctivitis presents as an acute follicular conjunctivitis, with a watery discharge and preauricular adenopathy. This conjunctivitis usually runs a 7- to 14-day course and is frequently accompanied by small corneal opacities. Epidemic keratoconjunctivitis can be differentiated from allergic conjunctivitis by the absence of pruritus, the presence of a mononuclear cellular response, and a follicular conjunctival response.

The treatment of viral conjunctivitis is usually supportive, although prophylactic antibiotics are frequently used. If significant corneal opacities are present, the application of topical steroid preparations has been suggested.

Acute Bacterial Conjunctivitis

The most prominent distinguishing feature of acute bacterial conjunctivitis is purulent discharge. Patients may also have a sensation mimicking a foreign body in the eye, and lid edema is not uncommon. The most common culprits are *Staphylococcal pneumonia, Haemophilus influenzae, S. aureus,* and *Moraxella catarrhalis*. Gonococcal conjunctivitis bears special mention because of the fact that it can be invasive and cause permanent damage. In gonococcal conjunctivitis, the typical symptoms are usually far more pronounced. There is often a very copious purulent discharge.

Treatment consists of warm compresses and ocular antibiotics. A follow-up visit within 2 days should be scheduled to check for progress.

Chlamydial (Inclusion) Conjunctivitis

In adults, inclusion conjunctivitis presents as an acute conjunctivitis with prominent conjunctival follicles and a mucopurulent discharge. There is usually no preceding upper respiratory infection or fever. This process occurs in adults who may harbor the chlamydial agent in the genital tract, but with no symptoms referable to this system. A nonspecific urethritis in men and a chronic vaginal discharge in women are common. The presence of a mucopurulent discharge and follicular conjunctivitis, which lasts more than 2 weeks, certainly suggests inclusion conjunctivitis. A Giemsa stain of a conjunctival scraping specimen may reveal intracytoplasmic inclusion bodies and helps to confirm the diagnosis. The treatment of choice is systemic tetracycline for 10 days.

Herpes Simplex Keratitis

Up to 500,000 cases of ocular herpes simplex are seen in the United States each year (100). A primary herpetic infection occurs subclinically in many patients. However, acute primary keratoconjunctivitis may occur with or without skin involvement. The recurrent form of the disease is seen most commonly. Patients usually complain of tearing, ocular irritation, blurred vision, and occasionally photophobia. Fluorescein staining of the typical linear branching ulcer (dendrite) of the cornea confirms the diagnosis. Herpetic keratitis is treated with antiviral compounds or by debridement. After the infectious keratitis has healed, the patient may return with a geographic erosion of the cornea, which is known as *metaherpetic (trophic) keratitis*. In this stage, the virus is not replicating, and antiviral therapy is usually not indicated. If the inflammation involves the deep corneal stroma, a disciform keratitis may result and may run a rather protracted course, leaving a corneal scar. The exact cause of disciform keratitis is unknown, but it is thought that immune mechanisms play an important role in its production (101,102). It is important to distinguish herpetic keratitis from allergic conjunctivitis. The absence of pruritus and the presence of photophobia, blurred vision, and a corneal staining area should alert the clinician to the presence of herpetic infection. Using corticosteroids in herpetic disease only spreads the ulceration and prolongs the infectious phase of the disease process (103).

Herpes Zoster

Herpes zoster can occur typically with the appearance of ocular symptoms as the

first manifestation, prior to the onset of skin involvement. Therefore, the diagnosis should always be kept in mind. The ocular symptoms occur when the ophthalmic division of the trigeminal nerve is involved. The presence of a vesicle at the tip of the nose (Hutchinson sign) may appear as a sentinel lesion. Like herpes infection, zoster also produces a dendritic keratitis. The distinction between the two, therefore, may be dependent on the typical skin lesions.

Keratoconjunctivitis Sicca

Keratoconjunctivitis sicca is a chronic disorder characterized by a diminished tear production. This is predominately a problem in menopausal or postmenopausal women and may present in patients with connective tissue disease, particularly rheumatoid arthritis. Although keratoconjunctivitis sicca may present as an isolated condition affecting the eyes only, it may also be associated with xerostomia (Sjögren syndrome).

Symptoms may begin insidiously and are frequently confused with a mild infectious or an allergic process. Mild conjunctival injection, irritation, photophobia, and mucoid discharge are present. Corneal epithelial damage can be demonstrated by fluorescein or rose Bengal staining, and hypolacrimation can be confirmed by inadequate wetting of the Schirmer test strip. Frequent application of artificial tears can be helpful. Cyclopsorin eye drops (Restasis) are indicated in patients not adequately responding to artificial tears.

Giant Papillary Conjunctivitis

Giant papillary conjunctivitis, which is characterized by the formation of large papillae (larger than 0.33 mm in diameter) on the upper tarsal conjunctiva, has been associated with the wearing of contact lenses, prostheses, and sutures (104). Although it is most commonly caused by soft contact lenses (105), it can also occur with gas-permeable and rigid lenses. Patients experience pruritus, excess mucus production, and discomfort when wearing their lenses. There is decreased lens tolerance, blurred vision, and excessive lens movement (frequently with lens displacement). Burning and tearing are also noted.

The patient develops papillae on the upper tarsal conjunctiva. These range from 0.3 mm to greater than 1 mm in diameter. The area involved correlates with the type of contact lens worn by the patient (105).

The mechanism of production of giant papillary conjunctivitis is unknown. One hypothesis is that the reaction is caused by an immunologic response to deposits on the lens surface. Deposits consist not only of exogenous airborne antigens but also of products in the tear film, such as lysozyme, IgA, lactoferrin,

and IgG (106,107). However, the amount of deposits does not clearly correlate with the presence of giant papillary conjunctivitis, and all lenses develop deposits within 8 hours of wear (107,108). More than two-thirds of soft lens wearers develop deposits within 1 year of wear. Evidence suggesting an immune mechanism in the production of giant papillary conjunctivitis is based on several observations. The condition is more common in atopic subjects. Patients with giant papillary conjunctivitis have elevated, locally produced tear IgE (109). Eosinophils, basophils, and mast cells are found in giant papillary conjunctivitis in greater amounts than in acute allergic conjunctivitis (109–113). There are elevated levels of major basic protein in conjunctival tissues of patients with giant papillary conjunctivitis (110) and elevated levels of leukotriene C_4, histamine, and tryptase in their tears (109–113). Further evidence for an IgE-mediated mechanism is the observation that ocular tissues from patients with giant papillary conjunctivitis exhibit increased messenger RNA for IL-4 and IL-5 (110) and have increased levels of major basic protein and eosinophilic cationic protein in tears (106–108).

Non-IgE-mediated immune mechanisms have also been incriminated in the production of this disorder. In fact, because the condition clearly occurs in nonallergic patients, other mechanisms must be a cause. For example, the tear cytokine profile in giant papillary conjunctivitis differs considerably from that found in vernal keratoconjunctivitis. It is clear, therefore, that microtrauma of the conjunctivitis is the major causative factor in this condition. Although eosinophils appear to play a strong role in vernal conjunctivitis and atopic keratoconjunctivitis, they seem to be less important in giant papillary conjunctivitis (110).

IgG levels are elevated, but the IgG is blood borne rather than locally produced (114). There is also evidence for complement activation, and there is decreased lactoferrin in the tears of patients with giant papillary conjunctivitis (108,114). Neutrophil chemotactic factor is present in tear fluids in amounts exceeding levels found in nonaffected soft contact lens wearers (112).

Treatment of giant papillary conjunctivitis is usually carried out by the ophthalmologist. Early recognition is important because discontinuation of lens wear early in the stage of the disease and prescription of appropriate lens type and edge design can prevent recurrence. It is also important to adhere to a strict regimen for lens cleaning and to use preservative-free saline. Enzymatic cleaning with papain preparations is useful to reduce the coating of the lenses by antigens. Disposable lenses may also be beneficial. Both cromolyn sodium and

nedocromil sodium have been found to be helpful (113).

Floppy Eye Syndrome

Floppy eye syndrome is a condition characterized by lax upper lids and a papillary conjunctivitis resembling giant papillary conjunctivitis. Men older than 30 years of age constitute the majority of patients. The condition is thought to result from chronic traction on the lax lid produced by the pillow at sleep. It may be unilateral or bilateral (115).

Vasomotor (Perennial Chronic) Conjunctivitis

Vasomotor, perennial, chronic conjunctivitis is a poorly defined condition not mediated by IgE. It refers to a conjunctivitis characterized by "vasomotor" instability. The term has been used to apply to patients who have chronic conjunctival findings exacerbated by irritant, and perhaps weather, stimulants in whom other disorders of the eye have been ruled out. It has been estimated that vasomotor stimuli may be involved in 25% of chronic conjunctivitis cases (116). It can be considered the ocular analogue of "vasomotor" rhinitis.

Approach to the Patient with an Inflamed Eye

The physician seeing a patient with acute or chronic conjunctivitis should first exclude diseases (not discussed in this chapter) that may be acutely threatening to the patient's vision. These include conditions such as acute keratitis, uveitis, acute angle-closure glaucoma, and endophthalmitis. The two most important symptoms pointing to a threatening condition are a loss in visual acuity and pain. These are signs that the patient could have an elevated intraocular pressure, keratitis, endophthalmitis, or uveitis. On physical examination, the presence of unreactive pupils and/or circumcorneal hyperemia (dilatation of the vessels adjacent to the corneal edge or limbus) are warning signals that indicate a potentially threatening problem, and require immediate ophthalmologic consultation. These findings, especially circumcorneal hyperemia, are present in four threatening conditions: keratitis, uveitis, acute angle-closure glaucoma, and endophthalmitis. This contrasts with the pattern of vasodilation seen in acute allergic conjunctivitis, which produces erythema that is more pronounced in the periphery and decreases as it approaches the cornea.

If the physician believes that the patient does not have a threatening eye disease, the next step is to differentiate between allergic and nonallergic diseases of the eye (Table 28.3). The differential diagnosis between allergic and nonallergic diseases of the eye can usually be made by focusing on a few key

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features. The following five cardinal questions should be asked in this regard:

1. Does the eye itch? This is the most important distinguishing feature between allergic and nonallergic eye disorders. All allergic conditions are pruritic. Nonallergic conditions usually do not itch. The physician must be certain that the patient understands what is meant by itching because burning, irritated, "sandy feeling" eyes are often described as "itchy" by the patient.

2. What type of discharge, if any, is present? A purulent discharge with early morning matting is not a feature of allergic disease and points toward infection.

3. Is the lid involved? Lid involvement indicates the presence of atopic dermatitis, contact dermatitis, or occasionally seborrhea or rosacea. Often, the patient complains of "eye irritation," which may mean the lid or conjunctiva or both. The physician should be careful to ascertain which area of the eye is involved.

4. Are other allergic manifestations present? Examples include atopic dermatitis, asthma, and rhinitis.

5. Are there other associated nonallergic conditions? Nonallergic conditions include dandruff and rosacea.

THE EAR: OTIC MANIFESTATIONS OF ALLERGY

The most common otologic problem related to allergy is otitis media with effusion (OME). The potential role of allergic disease in the pathogenesis of OME is explored in the following discussion.

Otitis media is a general term defined as any inflammation of the middle ear with or without symptoms and usually associated with an effusion. It is one of the most common medical conditions seen in children by primary care physicians (117). In 1996, it was estimated that total (direct + indirect) costs for otitis media in the United States approximated $5 billion (118). The classification of otitis media can be confusing. The First International Symposium on Recent Advances in Middle Ear Effusions includes the following types of otitis media: (a) acute purulent otitis media, (b) serous otitis media, and (c) mucoid or secretory otitis media. Chronic otitis media is a condition displaying a pronounced, retracted tympanic membrane with pathologic changes in the middle ear, such as cholesteatoma or granulation tissue. The acute phase of otitis media occurs during the first 3 weeks of the illness, the subacute phase between 4 and 8 weeks, and the chronic phase begins after 8 weeks. For this

review, *acute otitis media* (AOM) applies to the classic ear infection, which is rapid in onset and associated with a red, bulging, and painful tympanic membrane. Fever and irritability usually accompany AOM. The presence of middle ear fluid without signs or symptoms of acute infection is OME. In many of these patients, hearing loss (HL) accompanies the condition. Other commonly used names for OME are ear fluid, serous, secretory, or nonsuppurative otitis media. Chronic OME is persisting of OME for 3 months from the date of onset (if known) or from the date of diagnosis (if onset is unknown). Middle ear effusion is defined as fluid in the middle ear from any cause. Middle ear effusion is present with both OME and AOM, and may persist for weeks or months after the signs and symptoms of AOM resolve.

In the United States, there are about 2.2 million diagnosed episodes of OME occur annually in the United States at a cost of $4.0 billion (119). This condition results in the one of the most commonly performed surgeries in the United States: tympanostomy tube placement (118). OME is of major importance in children because the effusion can lead to a mild-to-moderate conductive HL of 20 dB or more (120). It has been theorized that chronic conductive HL in the child may lead to poor language development and learning disorders. When children aged 5 to 6 years in primary school were screened for OME, about one in eight were found to have fluid in one or both ears (121). There are many epidemiologic factors in the development of recurrent and chronic OME in children, with age at first episode being a major risk factor (122) (Table 28.4). Other risk factors include male sex, bottle feeding, day care attendance, allergy, race (Native American and Inuit), lower socioeconomic status, pacifier use, prone sleep position, winter season, and passive smoke exposure (118,123). In addition, diseases of the antibody-mediated immune system, primary ciliary dyskinesia, Down syndrome, and craniofacial abnormalities, especially cleft palate, can all contribute to chronic OME. In evaluation of the patient with recurrent or chronic OME, each of these conditions needs to be considered.

TABLE 28.3 DIFFERENTIAL FEATURES TO BE CONSIDERED IN DIAGNOSING ALLERGIC EYE DISEASE

CLINICAL FEATURE	SEASONAL	ITCHING	SCRATCHY (SANDY) IRRITATION	SKIN OF LIDS AND/OR MARGIN INVOLVED	BILATERAL
Acute allergic conjunctivitis	Yes	Prominent	Not usual	No	Yes

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Vernal conjunctivitis	Yes	Prominent	Not usual	No	Yes
Conjunctivitis sicca	No	No	Prominent	No	Yes
Acute viral conjunctivitis	Variable, usually is not	No	Variable	No	Variable
Acute bacterial conjunctivitis	No	No	Variable	Matting, lid edema	Variable
Contact	No	Yes	No	Variable	Usually

dermatoconjunctivitis				
Blepharoconjunctivitis (bacterial/seborrheic/rosacea)	No	No	No	Yes	Usually

These conditions are to be considered in the absence of significant pain, photophobia, vision loss or blurring, poorly reactive pupils, and/or a limbal flush (circum corneal hyperemia). Any of these manifestations can indicate an elevated intraocular pressure or the presence of uveitis or other threatening ocular conditions (see text).

Pathogenesis of Otitis Media with Effusion

It appears that multiple factors influence the pathogenesis of OME. Most studies link OME with eustachian tube dysfunction, viral and bacterial infections, abnormalities of mucociliary clearance, immature immune system, allergy, or as an inflammatory response following AOM, most often between 6 months and 4 years of age (Table 28.4).

Eustachian Tube Anatomy and Physiology

The nasopharynx and middle ear are connected by the eustachian tube. The production of middle ear effusions appears to be related to functional or anatomic abnormalities of this tube. Under normal conditions, the eustachian tube has three physiologic functions: (a) ventilation of the middle ear to equilibrate pressure and replenish oxygen; (b) protection of the middle ear from nasopharyngeal sound pressure and secretions; and (c) clearance of secretions produced in the middle ear into the nasopharynx.

The eustachian tube of the infant and the young child differs markedly from that of the adult. These anatomic differences predispose infants and young children to middle ear disease. In infancy, the tube is wide, short, and more horizontal in orientation. As growth occurs, the tube narrows, elongates, and

develops a more oblique course (Fig. 28.2). Usually, after the age of 7 years, these physical changes lessen the frequency of middle ear effusion (118). In the normal state, the middle ear is free of any significant amount of fluid and is filled with air. Air is maintained in the middle ear by the action of the eustachian tube. This tube is closed at the pharyngeal end except during swallowing, when the tensor veli palatini muscle contracts and opens the tube by lifting its posterior lip (Fig. 28.3A). When the eustachian tube is opened, air passes from the nasopharynx into the middle ear, and this ventilation system equalizes air pressure on both sides of the tympanic membrane (Fig. 28.3B).

TABLE 28.4 RISK FACTORS FOR CHRONIC AND RECURRENT OTITIS MEDIA WITH EFFUSION (OME)

1. Age—children with OME in the first year of life have increased incidence of recurrence

2. Males > females

3. Bottle-fed infants

4. Passive smoking exposure

5. Allergy

6. Lower socioeconomic status

7. Race—Native Americans and Eskimos > whites > African Americans

8. Day care centers

9. Season—winter > summer

10. Genetic predisposition—if siblings have OME, higher risk

11. Down syndrome
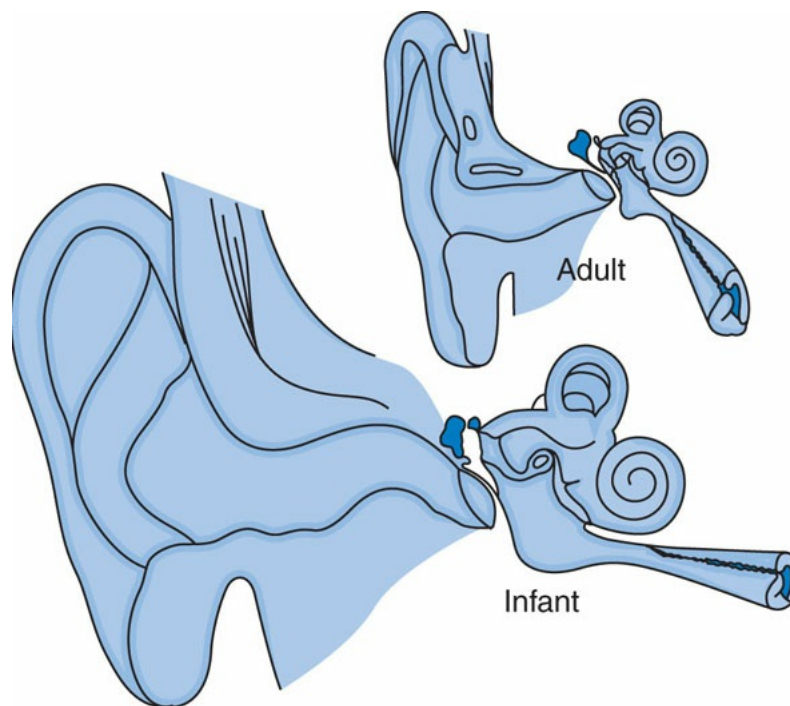
■ **FIGURE 28.2** Illustration showing difference in angles of eustachian tubes in infants and adults.

When the eustachian tube is blocked by either functional or anatomic defects, air cannot enter the middle ear, and the remaining air is absorbed. This results in the formation of negative pressure within the middle ear and subsequent retraction of the tympanic membrane (Fig. 28.3C). High negative pressure associated with ventilation may result in aspiration of nasopharyngeal secretions into the middle ear, producing acute OME (Fig. 28.3D). Prolonged negative pressure causes fluid transudation from the middle ear mucosal blood vessels (Fig. 28.3E). With chronic OME, there is infiltration of lymphocytes and macrophages, along with production of different inflammatory mediators. Also, there is an increased density of goblet cells in the epithelium of the eustachian tube. It is thought that many children with middle ear effusions, without a demonstrable cause of eustachian tube obstruction, have a growth-related inadequate action of the tensor veli palatini muscle. Another possibility is functional obstruction from persistent collapse of the tube owing to increased

tubal compliance.

Nasal obstruction, either from adenoid hypertrophy or from infectious or allergic inflammation, may be involved in the pathogenesis of middle ear effusion by the Toynbee phenomenon (124). Studies have reported that, when the nose is obstructed, there is an increased positive nasopharyngeal pressure followed by a negative nasopharyngeal pressure on swallowing. The increased positive nasopharyngeal pressure may predispose to insufflation of secretions into the middle ear, and the secondary negative pressure in the nasopharynx may further be a factor in the inadequate opening of the eustachian tube, thereby causing obstruction.
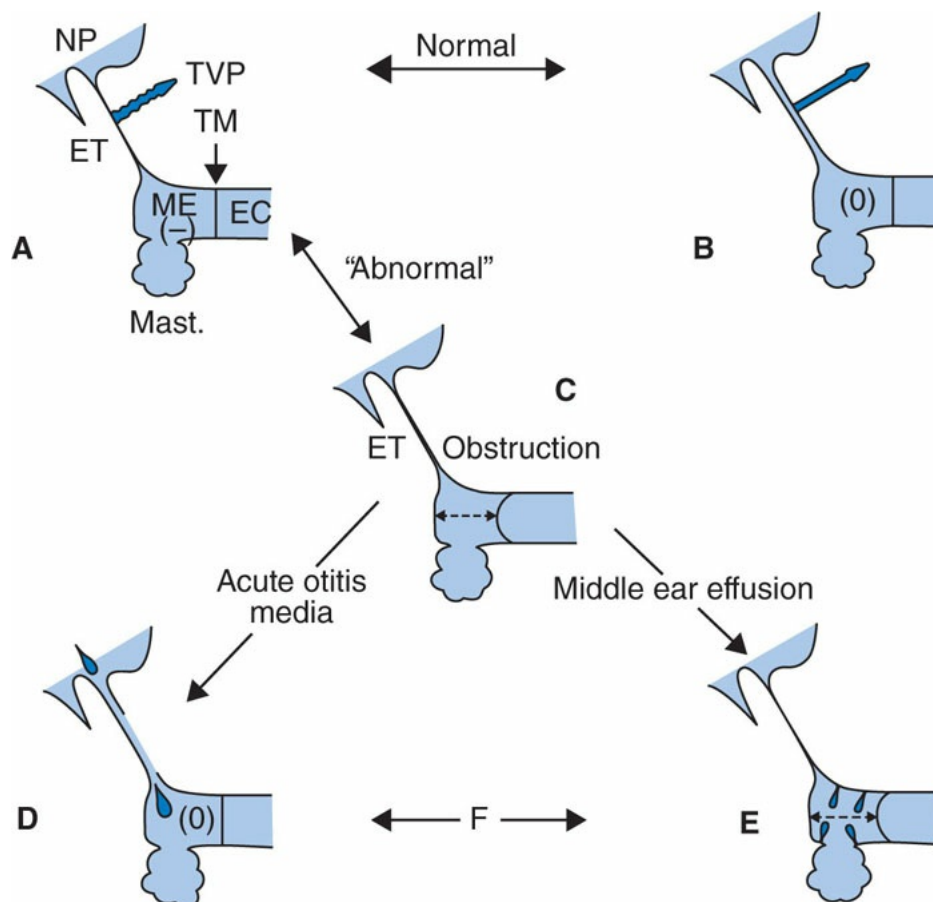
■ FIGURE 28.3 Proposed pathogenic mechanisms of middle ear effusion. EC, external canal; ET, eustachian tube; Mast., mastoid; TM, tympanic membrane; ME, middle ear; NP, nasopharynx; TVP, tensor veli palatini muscle. (From Bluestone CD. eustachian tube function and allergy in otitis media. *Pediatrics* 1978;61:753, with permission.)

Infection

Respiratory bacterial and viral infections are significant contributors to the pathogenesis of otitis media. Bacteria have been cultured in about 70% of middle

ear effusions during tympanocentesis for otitis media in children (125). The three most common bacterial isolates in AOM and OME are *Streptococcus pneumoniae*, nontypeable *H. influenzae* (NTHI), and *M. catarrhalis* (118). *S. pyogenes* and anaerobic cocci are isolated in less than 5% of the patients with AOM. In 1999, *Alloiococcus otitis* was noted to be a significant bacterial pathogen in relationship with OME (126). The predominant anaerobes are Gram-positive cocci, pigmented *Prevotella* and *Porphyromonas* species, *Bacterioides* species, and *Fusobacterium* species. The predominant organisms isolated from chronic otitis media are *Staphylococcus aureus, Pseudomonas aeruginosa*, and anaerobic bacteria. In neonates, group B streptococci and Gram-negative organisms are common bacterial pathogens causing otitis media. Most patients with chronic OME have sterile middle ear effusions.

Post and associates used a polymerase chain reaction (PCR) to detect bacterial DNA in middle ear effusions in children who had failed multiple courses of antibiotics and, therefore, were undergoing myringotomy and tube placement (127). Of the 97 specimens, 75 (77.3%) were PCR positive for one or more of the following bacteria: *S. pneumoniae*, NTHI, and *M. catarrhalis*. This suggests that active bacterial infection may be occurring in many children with chronic OME.

Viral agents are not commonly cultured from middle ear effusions. Most studies report positive viral cultures in less than 5% of the aspirates from the middle ear, with respiratory syncytial virus (RSV) being the most common isolate (128). However, using molecular techniques such as PCR, viral RNA can be detected in about 75% of children with AOM; common isolates include rhinovirus, coronavirus, and RSV (129,130).

Mucociliary Dysfunction

Mucociliary dysfunction from either a genetic defect or an acquired infectious or environmental condition can lead to OME. Investigations suggest that the mucociliary transfer system is an important defense mechanism in clearing foreign particles from the middle ear and the *eustachian tube* (131). Goblet and secretory cells provide a mucous blanket to aid ciliated cells in transporting foreign particles toward the nasopharynx for phagocytosis by macrophages, or to the lymphatics and capillaries for clearance. Respiratory viral infections are associated with transient abnormalities in the structure and function of cilia (132). Primary ciliary dyskinesia, an autosomal recessive syndrome, has been linked to more than 20 different structural defects in cilia, which lead to ciliary dysfunction (133). Both of these conditions can lead to inefficient ciliary

transport, which results in mucostatics and can contribute to *eustachian tube* obstruction and the development of middle ear effusion.

Allergy and Immunology

There is considerable debate about whether allergic disorders are a factor in the pathogenesis of OME. Many investigators believe that allergic disorders play a prominent role, either as a cause or contributory factor; whereas others state that there is no convincing evidence that allergy leads to otitis media. Allergy has been implicated as a causative factor in OME by (a) double-blind placebo-control nasal challenge studies with histamine and allergens; (b) studies on allergic children; and (c) studies on randomly selected children with OME referred to specialty clinics (134,135). Kraemer (136) compared risk factors of OME among children with tympanostomy tubes compared with controls matched for age and reported atopy as a risk factor. In a series of 488 new patients referred to a pediatric allergy clinic, 49% had documented middle ear dysfunction (137). In a prospective study, Bierman and Furukawa (138) have demonstrated that allergic children have a high incidence of OME with conductive HL. Half of their patients developed chronic OME or AOM in a 6-month follow-up. Tomonaga et al. evaluated 605 children with allergic rhinitis and found 21% with OME. They also determined that 50% of 259 children with diagnosed OME had allergic rhinitis (139). Bernstein and Reisman reviewed the clinical course of 200 randomly selected children with OME who had at least one tympanostomy with tube insertion (140). Twenty-three percent were considered allergic by history, physical examination, and allergy skin testing.

In human studies, Friedman et al. evaluated eight patients, aged 18 to 29 years, with seasonal rhinitis but no middle ear disease. Patients were blindly challenged with the pollen to which the patient was sensitive or to a control. Nasal function was determined by nasal rhinomanometry and eustachian tube function by the nine-step-deflation tympanometric test. The results from this and other studies (141) showed that eustachian tube dysfunction can be induced by allergen and histamine challenge (141), although no middle ear effusions occurred. Osur evaluated 15 children with ragweed allergy and measured eustachian tube dysfunction before, during, and after a ragweed season (142). There was a significant increase in eustachian tube dysfunction during the pollen season, but it did not lead to OME. It appears that other variables need to be present for effusion to develop.

Work by Hurst et al. has provided the most conclusive evidence of the role of allergy in OME. These researchers evaluated 89 patients for allergy who

required the placement of tympanostomy tubes because of persistent effusion. Radioallergosorbent test, serum IgE levels, and skin tests were performed. Atopy was present in 97% of the patients with OME by skin testing. Significant levels of eosinophil cationic protein and eosinophils were found in the effusions, suggesting allergic inflammation in the middle ear (143). These investigators also determined that IgE in middle ear effusion is not a transudate but more likely reflects an active localized process in atopic patients (144) and that tryptase, a reflection of mast cell activity, is found in most ears of patients with chronic effusion who were atopic (145). These findings and others (146) support the hypothesis that middle ear mucosa is capable of an allergic response and that the inflammation within the middle ear of most OME patients is allergic in nature.

AOM and chronic suppurative otitis media are commonly part of a primary or secondary immunodeficiency syndrome. The middle ear is usually one of many locations for infection in immunodeficient patients. Of the primary immunodeficiency conditions, otitis media is more common in the humoral or B-cell disorders, such as X-linked hypogammaglobulinemia, common variable immunodeficiency, and selective IgA deficiency. A patient's incapacity to produce antibodies against pneumococcal polysaccharide antigens and a related IgG_2 subclass deficiency has been associated with the development of recurrent otitis media in children (147).

Diagnosis

AOM usually presents with fever, otalgia, vomiting, diarrhea, and irritability. In young children, pulling at the ear may be the only manifestation of otalgia. Otorrhea, discharge from the middle ear, may occur if spontaneous perforation of the tympanic membrane occurs. It is not uncommon for AOM to be preceded by an upper respiratory infection. The pneumatic otoscope is an important tool for making accurate diagnosis of AOM. Classically, the tympanic membrane is erythemic and bulging without a light reflex or the ossicular landmarks visualized. Pneumatic testing fails to elicit any movement of the tympanic membrane on applying positive and negative pressures.

Most children with OME do not have symptoms. Others may complain of stopped-up or popping ears or a feeling of fullness in the ear. Older children may even note an HL. Their teachers and parents detect the condition in many younger children because they are noted to be inattentive, loud talkers, and slow learners. Other children may be discovered with OME in screening tests done for

hearing at school. When middle ear effusions become chronic, there may be significant diminution of language development and auditory learning, with resultant poor academic achievement. On pneumatic otoscopic examination of patients with OME, the tympanic membrane may appear entirely normal. At other times, air–fluid levels and bubbles may be apparent. There is often retraction of the tympanic membrane, and the malleus may have a chalky appearance. As the disease progresses, the tympanic membrane takes on an opaque amber or bluish gray color. Alteration of the light reflex is commonly present. Mild retraction of the tympanic membrane may indicate only negative ear pressure without effusion. In more severe retraction, there is a prominent lateral process of the malleus with acute angulation of the malleus head. Tympanic membrane motility is generally poor when positive and negative pressures are applied by the pneumatic otoscopy.

Tympanometry is commonly used as a confirmatory test for OME. It is a tool for indirect measuring of the compliance or mobility of the tympanic membrane by applying varying ear canal pressure from 200 to 400 mm H_2O. Patients with OME have a flat (type B) curve because of failure of the tympanic membrane to move with the changing pressure. Audiometric examination in OME often discloses a mild-to-moderate degree of conduction hearing impairment of 20 to 40 dB. The guidelines for the treatment of OME in young children from the Agency for Health Care Policy and Research recommend that an otherwise healthy child with bilateral OME for 3 months should have a hearing evaluation (148). According to a recent update on the clinical practice guidelines by the American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAOHNSF), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP), the physician should obtain an age-appropriate hearing test if OME persist for 3 months or longer or for OME of any duration in an at-risk child (149). Counsel families of children with bilateral OME and documented HL about the potential impact on speech and language development is also recommended. Physician should follow up a child with chronic OME at 3 to 6 months' interval until the effusion is no longer present.

Acoustic reflectometry, a test that involves a tone sweep in the patient's ear and measuring reflected sound pressure to assess effusion, and tuning fork tests can also be used in the diagnosis and evaluation of OME.

The physical examination of the patient with OME should not stop at the tympanic membrane. Craniofacial anomalies, such as Down syndrome, submucous cleft palate, and bifid uvula, may be present that predispose to OME.

Stigmata of an allergic diathesis should be sought in each patient. Eye examination may illustrate injected conjunctiva seen in patients with allergic conjunctivitis. Pale, boggy turbinates with profuse serous rhinorrhea are commonly found with allergic rhinitis. When chronic middle ear effusions are associated with the signs and symptoms of allergic disease, a standard allergic evaluation is indicated. A nasal smear for eosinophils, peripheral eosinophil count, and cutaneous tests for specific allergens may be of diagnostic importance.

In patients with recurrent or chronic otitis media in whom middle ear disease is just one of many sites of infection, screening of the immune system should be considered. Laboratory studies, such as IgG, IgA, and IgM, naturally occurring antibodies such as isohemagglutinins, and specific antibody titers to antigens previously given in vaccines, such as tetanus, are useful in evaluation of humoral immune status. Measuring specific antibody levels before and after administration of a pneumococcal polyvalent vaccine is an effective mean of evaluating humoral immune function. Another possible condition to consider in children with multiple sites of recurrent infection is primary ciliary dyskinesia. Examination of the cilia by electron microscopy can illustrate abnormalities of the cilia ultrastructure, which can lead to ciliary dysfunction and its related chronic otitis.

Management

Management of the patient with OME requires appropriate pharmacologic and surgical intervention. It is important to understand the natural history of AOM and OME. Usually, the symptoms of AOM resolve in 48 to 72 hours if the organism is sensitive to the prescribed antibiotic. Two weeks into treatment, 70% of patients have a middle ear effusion. One month after treatment, 40% continue to have effusion, but after 3 months, only 10% of patients continue to have a persistent effusion (118). In patients with OME in which allergy may be a contributing factor, appropriate allergy treatment of avoidance of particular allergens, medication, and immunotherapy may be indicated.

Pharmacotherapy

Antimicrobial agents are the first-line therapy in AOM and may be beneficial in OME because bacteria are found in many cases. Amoxicillin is recommended as the first-line agent to treat uncomplicated AOM. For clinical treatment failures after 2 to 3 days of amoxicillin, recent use of amoxicillin in the last 30 days, concurrent purulent conjunctivitis, or with a history of recurrent AOM

unresponsive to amoxicillin, the AAP Clinical Practice Guidelines recommend antimicrobial agents with additional β-lactamase coverage, including oral amoxicillin/clavulanate, cefuroxime axetil, cefprozil, cefpodoxime proxetil, and intramuscular ceftriaxone (150). Intramuscular ceftriaxone should be reserved for severe cases or patients in whom noncompliance is expected. Tympanocentesis for identification of pathogens and susceptibility to antimicrobial agents is recommended for selection of third-line agents (150). Resistant bacteria are an increasing problem in the management of children with otitis media. Sutton et al. reported penicillin resistance in the middle ear fluid of 38.2% of *S. pneumoniae* cultures at the time of tympanostomy tube surgery (151). β-Lactamase production was found in 65.1% and 100% of *H. influenzae* and *M. catarrhalis* specimens, respectively, in that study.

In a recent review van Zon et al. reviewed 23 studies to evaluate the benefit of antibiotics use for the treatment of OME. The reviewers reported only a small advantage of antibiotics with complete resolution of the effusion (152). There was no significant impact on HLs or the rate of subsequent tympanostomy tube insertion. As a conclusion, antibiotics are not recommended to treat OME, because of the small benefits that are offset by adverse events, bacterial resistance, and lack of impact on HLs or future surgery (152). In some circumstances, like acute bacterial sinusitis or group A streptococcal infection, antibiotic therapy can be beneficial. A recent review by Venekamp et al., which involved 23 trials, evaluated the benefits and harms of antibiotics in treatment of OME. The evidence shows that oral antibiotics are associated with an increased chance of complete resolution of OME at various time points, but the results indicate that antibiotic use is associated with adverse events, such as diarrhea, vomiting, or skin rash. There is no short-term hearing benefit, no change in frequency of ventilation tube insertions, and no benefit on other outcomes such as speech, language and cognitive development, or quality of life (153). Another management option advocated for OME is observation of the patient for up to 4 months because of the natural history of resolution of OME in most patients. In patients with recurrent episodes of otitis media, a prophylactic antibiotics is no longer recommended, rather a tympanostomy tube can be offered to a patient with three episodes in 6 months or four episodes in 1 year (with one episode in the preceding 6 months) (150,154).

Another therapeutic modality prescribed in patients with OME is oral corticosteroids. Many studies have evaluated corticosteroids alone and in combination with antibiotics in clearing of middle ear effusions. The recent clinical practice guidelines from the AAO-HNS, AAP, and AAFP indicate that

systemic corticosteroid therapy is not effective in treating these children (149). In a recent systematic review to evaluate the benefit of an oral steroid and intranasal steroid, either alone or in combination with antibiotics in management of OME, Simpson et al. conclude that oral steroids, especially when used in combination with an oral antibiotic, lead to a quicker resolution of OME in the short term (155). However, there was no evidence of longer term benefit and no impact on relieve symptoms of HL. There was also no significant evidence of benefit from topical intranasal steroids, alone or in combination with an antibiotic, either at short- or longer-term follow up (155). Williamson et al. evaluated the benefit of topical intranasal corticosteroids for bilateral OME in a double-blind randomized control trial. The study included 127 children aged 4 to 11 years, The results showed no difference in the resolution of effusion or HL over 3 months between children treated with nasal mometasone 50 μ in each nostril or placebo (156). In patients with allergic rhinitis complicated by OME, topical nasal steroids can be beneficial, because of the anti-inflammatory effect on allergic rhinitis, which may be a contributing factor to OME (157). In a systematic review of randomized controlled trials, to evaluate the short- and long-term benefit of antihistamines and/or decongestants for treating OME, Griffin and Flynn (158) concluded that there was no significant benefit on OME resolution. Schoem et al. evaluated the role of montelukast in treatment of OME in a prospective randomized placebo-controlled double-blind study, involving children aged 2 to 6 years with one or bilateral OME. Early results shows no advantage of montelukast versus placebo in clearance of middle ear effusion (159). Another study by Ertugay et al. evaluated the use of montelukast, 4 mg, with or without the H_1 antihistamine, levocetirizine, 2.5 mg/5 mL, in 120 children with OME in a randomized prospective double-blind placebo-controlled, four treatment arm, trial. The results showed significant improvement in otoscopic sign scores for subjects using both therapies. Improvement in bilateral tympanometry findings was not significant (160). At present, the data do not support the use of systemic corticosteroids, intranasal corticosteroids, antihistamines, or decongestants in the management of OME as discussed earlier.

Environmental Control

When allergic rhinitis is associated with OME, environmental control of allergens and irritants should be advised. The most significant irritant is cigarette smoke. The parents must be urged to avoid exposure of their children to cigarette smoke in the home, car, restaurant, and day care facilities. Environmental inhalant allergens are more important to younger children because of the greater

time spent in the home. Specific instructions for the avoidance of house dust mites, cockroaches, animal dander, and house mold spores should be given when indicated.

Vaccination

The heptavalent pneumococcal conjugate vaccine has been effective in significantly decreasing the number of episodes of otitis media in children. Black et al. demonstrated that children who received the pneumococcal conjugate vaccine were 20.1% less likely to require insertion of tympanostomy tubes than were controls (161). It is estimated to prevent up to 1,000,000 episodes of AOM per year, leading to cost savings of $160 per otitis media episode prevented (162). Similar results have been reported by Canadian investigators (163).

Surgical Treatment

Refractory cases that continue to have middle ear fluid after a 3- to 6-month trial of observation or medical management often need surgical intervention. Chronic middle ear effusion has been associated with the development of cholesteatomas, atrophy of the tympanic membrane, facial paralysis, and retention pockets. The Agency of Health Care Policy and Research Guidelines recommend myringotomy with the insertion of tympanostomy tubes for children with OME between 1 and 3 years of age who have bilateral HL of at least 20 dB for 4 to 6 months. This procedure is effective in removing the effusion and restoring normal hearing in the child. A number of studies (118,164) have demonstrated the beneficial effect of tympanostomy tubes in OME. It is usually recommended that tympanostomy tubes remain in place for 6 to 18 months. The longer the tube remains in the tympanic membrane, the greater the chance of complications. These include tympanosclerosis, persistent perforation, otorrhea, and occasionally cholesteatoma. Adenoidectomy has been suggested in the treatment of OME to remove blockage of the *eustachian tube* and improve ventilation. The Agency of Health Care Policy and Research Guidelines do not recommend adenoidectomy for children between 1 and 3 years of age with OME, although older children may benefit from the surgery. The AAOHNSF, AAP, and AAFP clinical practice guidelines recommend tympanostomy tubes when surgery is performed for OME in a child less than 4 years of age (149). Adenoidectomy should not be performed unless a distinct indication, such as nasal obstruction or chronic adenoiditis, exists. For a child older than 4 years of age, tympanostomy tubes or adenoidectomy or both are recommended when surgery is performed for OME. The primary benefits of adenoidectomy are to reduce failure rates, reduce time with middle ear effusion, and decrease the need for repeat surgery or future

tubes. Gates et al. demonstrated that adenoidectomy improved and reduced recurrence of OME in children older than 4 years of age (165). They reported that the size of the adenoids did not relate to improvement of OME with adenoidectomy. One study showed that the use of CO_2 laser myringotomy was more efficacious than incisional myringotomy with adenoidectomy in OME (166). Tonsillectomy is not recommended in the management of children with OME (118,167).

Immunotherapy

Subcutaneous or sublingual immunotherapy has been proved to be effective in the therapy for allergic rhinitis, when avoidance of the allergen is not possible or the symptoms are uncontrolled by medication. Many have the clinical impression that SCIT may be of help in OME in children with allergic rhinitis. However, there have been no controlled studies to verify this clinical impression.

In conclusion, the prognosis in OME is usually good. As the child gets older, the incidence of OME tends to decrease. The medical and surgical intervention outlined for OME helps to control the condition until the child "outgrows" this disease.

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Cutaneous Allergic Diseases

Atopic Dermatitis
PECK Y. ONG AND DONALD Y. M. LEUNG

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease in children and adults (1). The disease is characterized by skin dryness, itch, flexural involvement in older children and adults, and facial/extensor involvement in infants (Fig. 29.1). Infections are a major morbidity of AD. These infections are caused by *Staphylococcus aureus, Streptococcus pyogenes*, herpes simplex virus (eczema herpeticum [EH]), enterovirus (eczema coxsackium [EC]), and smallpox vaccinia virus vaccine (eczema vaccinatum [EV]). They may lead to life-threatening complications that require urgent care visits and hospitalizations.

Chronic AD negatively impacts the quality of life of patients, particularly in those with moderate-to-severe disease. Patients are affected by sleep disturbances and fatigue (2). Parents of AD children are among the most affected parents who take care of children with chronic illness in terms of sleep disturbances and stress (3,4). Sleep deprivation and fatigue lead to poor school or work performance, social isolation, anxiety, and depression in both patients and parents. The national annual cost of AD has been estimated to be $5.3 billion/year (5). There have been significant advances in our understanding of

the pathogenesis and treatment of AD in recent years. This chapter outlines the current treatment approach and potential new managements in the prevention and treatment of AD.

EPIDEMIOLOGY AND NATURAL HISTORY

The prevalence of AD is increasing around the world in different regions in the United States. AD prevalence in children ranges from 9% to 18% among states and districts (6). About 30% of these children have allergic rhinitis, whereas 25% have asthma. Although AD is primarily a childhood disease, it also has significant impact on adults. Recent estimate of the prevalence of adult AD in the United States is about 7% (5). The majority (80%) of these adult AD patients have childhood-onset AD, but 20% have adult-onset AD. More than 50% of AD patients have onset before a year, and most AD patients (80%) have onset by 7 years. The majority of children with AD have no more AD by 11 years; however, a significant 35% continues to have AD. Early age of onset and moderate-to-severe disease are the major risk factors for the persistence of AD (7).

■ FIGURE 29.1 Facial and extensor distribution of infantile atopic dermatitis.

■ PATHOGENESIS

The pathogenesis of AD involves a combination of skin barrier defects, immune dysregulation, and infectious agents (1). Although AD has been linked to filaggrin mutations, a protein that has skin barrier functions, only a minority of AD patients carries these mutations. In addition, more than half of individuals with filaggrin mutations do not have AD. These observations suggest that other skin barrier genes or variants in the immune response are responsible for the pathogenesis of AD. Genetic variants of thymic stromal lymphopoietin (TSLP) have been associated with AD and EH (8). TSLP is an important cytokine that induces T_H2 responses. Importantly, expression of TSLP in infant skin precedes development of clinical AD (9). It is produced by keratinocytes. Together with

interleukin (IL)-33 and IL-25, it activates type 2 innate lymphoid cells that produce IL-4, IL-5, and IL-13. These cytokines lead to further downstream activation of T_H2 cells and amplification of IL-4, IL-5, and IL-13 production. These cytokines and IL-31, a cytokine that induces itch, are expressed in acute AD lesions. In addition to these cytokines, adults with chronic AD lesions are characterized by increased expression of IL-22 (10). IL-22 leads to hyperplasia of keratinocytes and further skin barrier defects. IL-4 and IL-13 have also been known to suppress the expression of filaggrin, leading to skin barrier defects (8). Genetics may also be a predispositing factor for AD patients to have increased infections. Multiple genetic variants in the type I and II interferon pathways have been associated with an increased risk for EH (8). *S. aureus* is a known trigger for AD symptoms. This bacteria is capable of producing multiple toxins, including α/δ cytolysins and enterotoxins (superantigens), which induce T_H2 inflammation in AD. A reduced skin innate immunity and the presence of myeloid-derived suppressor cells, which suppress T-cell immunity (11), further contribute to the increased risk of skin infections in AD.

DIAGNOSIS

AD consists of many phenotypes. In the future, it may be possible to use genetic testing or biomarkers to identify these phenotypes. However, currently, the diagnosis of AD is based on clinical assessment. Itch must be present. In addition, dry skin, flexural (or facial/extensor in infants) distribution of eczema, and the presence of personal or family history of atopy are important features of the diagnosis (see Table 29.1). The presence of multiple food allergies or specific food immunoglobulin E (IgE) sensitization in young children with eczema is consistent with the diagnosis of AD. In patients with adult-onset AD, they may have atypical features, including nummular dermatitis, seborrheic dermatitis, hand/face/neck dermatitis, and lichenified eczema on the trunk. However, if eczema is generalized or unresponsive to therapy, a skin biopsy or other diagnostic work-up should be considered to rule other skin diseases, such as cutaneous T-cell lymphoma or immunodeficiency. Table 29.2 shows the differential diagnosis of AD.

TABLE 29.1 DIAGNOSTIC CRITERIA FOR ATOPIC DERMATITIS

The presence of itchy skin in the past 12 mo, plus three of more of the following:

1. Onset of the skin condition under 2 y (not used in children under 4 y)

1425

2. History of itchy skin involving flexural areas (elbows, behind the knees, front of ankles, or around the neck)

3. History of generalized dry skin

4. Personal history of asthma or allergic rhinitis (for children under 4 y, history of atopic disease in a first-degree relative may be included)

5. Visible flexural dermatitis

Williams HC, Burney PG, Pembroke AC, et al. The U.K. Working Party's diagnostic criteria for atopic dermatitis. III. Independent hospital validation. *Br J Dermatol*. 1994;131:406–416.

TABLE 29.2 DIFFERENTIAL DIAGNOSES OF ATOPIC DERMATITIS

Dermatologic Diseases

Seborrheic dermatitis, irritant or allergic contact dermatitis, psoriasis, nummular dermatitis, lichen simplex chronicus, pityriasis rosea, ichthyos

Neoplastic Diseases

Cutaneous T-cell lymphoma (mycosis fungoides, Sézary syndrome), Letterer–Siwe disease (Langerhans cell histocytosis), necrolytic migratory erythema associated with pancreatic tumor

Immunodeficiencies

Hyper-IgE syndrome, Dock 8 deficiency, Wiskott–Aldrich syndrome, severe combined immunodeficiency, Omenn syndrome, IPEX (immune dysregulation, polyendocrinopathy, enteropathy X-linked) syndrome

Infectious Diseases

Human immunodeficiency virus–associated eczema, scabies, candidiasis, tinea versicolor

Congenital and Metabolic Disorders

Netherton syndrome, phenylketonuria, acrodermatitis enteropathica, essential fatty acid

deficiency, biotin deficiency, infantile-onset multiple carboxylase deficiency

Krol A, Krafchik B. The differential diagnosis of atopic dermatitis in childhood. *Dermatol Ther*. 2006;19:73–82.

CLINICAL EVALUATION AND MANAGMENT

Evaluation of Severity

In the clinical setting, the severity of AD is graded based on history and physical examination. Patients with generalized eczema, history of hospitalization or urgent care visits for AD, history of requirement for systemic corticosteroids or immunosuppressants, recurrent infections or EH, and involvement of face, hands, or eyes are generally considered to have moderate-to-severe AD. Most validated scoring systems for AD severity, such as SCOring of Atopic Dermatitis (SCORAD) and Eczema Area and Severity Index, may be too time-consuming to be used in the clinical setting. However, clinicians may consider the simpler Three Item Severity score (Table 29.3) or Patient-Oriented Eczema Measures, which are based on a simplified version of SCORAD and patient-based symptoms, respectively, for more objective measurement of AD severity. Another patient-based AD severity measurement is Patient-oriented SCORAD, which is available on phone apps for use by clinicians and patients. An accurate assessment of AD severity is crucial for assessing treatment progress and may dictate the management; for example, for moderate-to-severe AD patients, treatment with at least a mid-potency topical corticosteroid (TCS), referral to specialists, or work-up for food allergy (in young children) should be considered.

TABLE 29.3 THREE ITEM SEVERITY (TIS) SCORE

	MILD	MODERATE	SEVERE
Total score	0–2	3–5	6–9

The TIS is the sum of the three items (3 "e"s): erythema, edema, and excoriations (scored on a scale from 0 to 3); each item should be scored on the most representative lesion, that is, a lesion which represents the average severity.

Willemsen MG, van Valburg RW, Dirven-Meijer PC, et al. Determining the severity of atopic dermatitis in children presenting in general practice: an easy and fast method.

Routine Daily Skin Care

Skin hydration and daily application of moisturizers are recommended as a preventive treatment in most AD guidelines. However, there is no consensus on the method and frequency of skin hydration. Our clinical experience and past studies (12,13) have shown that daily bath or shower for 15 to 20 minutes followed by application of topical moisturizer and/or medications is an effective method of skin hydration. Such preventive care is crucial to restoring skin barrier function in AD patients.

Topical Corticosteroids

TCS remain first-line treatment for AD. Table 29.4 shows some of the common TCS in different potencies. For mild AD, low-potency TCS (groups VI and VII) may suffice. But for moderate-to-severe AD, mid-potency TCS (e.g., groups IV and V) should be prescribed in adequate quantity. Concerns for the side effects of TCS and noncompliance are a main reason for treatment failure in AD. In spite of numerous studies showing the efficacy and safety of TCS in AD (14–16), adherence with TCS remains poor. These problems often arise from unfounded fears for the side effects of TCS (17). Recent concern for TCS "withdrawal" (or "addiction") has resulted in patients' or parents' refusal to use TCS. This has led to AD flare, skin infections, and hospitalization. This poorly defined condition has been reported mostly in adults on the face and genital areas after prolonged use of moderate to high-potency TCS (18). Skin lesions caused by TCS withdrawal and AD are indistinguishable based on histologic examination. In addition, there may be overlapping features between TCS withdrawal and rosacea. In spite of the low quality of evidence for the existence of this condition, only 0.3% has been reported in patients younger than 3 years. Patients should be educated on the difference between systemic corticosteroids versus TCS and their side effects. Most patients and parents are confused on how much TCS to apply. The fingertip unit method offers a practical and reassuring guide for patients and parents to apply TCS (Table 29.5 and Fig. 29.2). Patients are educated on applying TCS on affected areas twice daily as needed. Select AD patients may benefit from a proactive approach by applying TCS on unaffected areas that previously flared or of potential flare twice weekly. This approach has been shown to reduce the overall flare and need for TCS in AD (19).

Management of Itch, Pain, and Sleep

Itch and sleep problem remain to be a major morbidity of AD. These problems often persist in many AD patients even years after they have outgrown AD. The first-generation antihistamines, such as diphenhydramine and hydroxyzine, do not stop the itch in AD. Their main effect is sedation. They are, therefore, best used before sleep. Nonsedative second-generation antihistamines, such as loratadine or cetirizine, have not been proven to be effective in AD, although they can be helpful in the 10% AD with chronic urticaria. There is anecdotal evidence that oral doxepin at low dose may improve the itch and sleep of AD patients, but further studies are needed to validate this. Pain not associated with fissures, skin cracks, or infection is an emerging problem in AD (20). AD patients may complain of pain, burning, and stinging on unaffected areas. Further studies are needed to clarify the mechanisms of these symptoms and whether medications, such as gabapentin or pregabalin, are beneficial. Because there are overlapping mechanisms between itch and pain, systemic and topical μ opiod receptor antagonists have been studied in AD, but have been met with mixed results. On the other hand, κ opiod receptor agonists are potential treatment for the itch of AD. This medication has been approved for use in Japan for itch associated with renal disease and is currently in phase 2 clinical trials for AD. Other potential anti-itch medications include monoclonal antibody against IL-31, which is produced by T_H2 cells and has been shown to be an important mediator of itch.

TABLE 29.4 TOPICAL CORTICOSTEROID POTENCIES

GROUP I (most potent)

Betamethasone dipropionate 0.05% (Diprolene) (cream, ointment)

Diflorasone diacetate 0.05% (Psorcon) (ointment)

Clobetasol propionate 0.05% (Temovate) (cream, ointment)

Halobetasol dipropionate 0.05% (Ultravate) (cream, ointment)

GROUP II

Amcinonide 0.1% (Cyclocort) (ointment)

Betamethasone dipropionate 0.05% (Diprosone) (cream, ointment)

Mometasone furoate 0.1% (Elocon) (ointment)

Halcinonide 0.1% (Halog) (cream)

Fluocinonide 0.05% (Lidex) (gel, cream, ointment)

Desoximetasone (Topicort) (0.05% gel, 0.25% cream, ointment)

GROUP III

Fluticasone propionate 0.005% (Cutivate) (ointment)

Amcinonide 0.1% (Cyclocort) (lotion, cream)

Diflorasone diacetate 0.05% (Florone) (cream)

Betamethasone valerate 0.1% (Valisone) (ointment)

GROUP IV

Mometasone furoate 0.1% (Elocon) (cream)

Triamcinolone acetonide 0.1% (Kenalog) (cream)

Fluocinolone acetonide 0.025% (Synalar) (ointment)

GROUP V

Fluticasone propionate 0.05% (Cutivate) (cream)

Fluocinolone acetonide 0.025% (Synalar) (cream)

Desonide 0.05% (Tridesilon) (ointment)

Betamethasone valerate 0.1% (Valisone) (cream)

Hydrocortisone valerate 0.2% (Westcort) (cream)

GROUP VI

Alclometasone dipropionate 0.05% (Aclovate) (cream, ointment)

Flucinolone acetonide 0.01% (Synalar) (solution, cream)

Desonide 0.05% (Tridesilon) (cream and aqueous gel)

GROUP VII (least potent)

Hydrocortisone 1%/2.5% (Hytone) (lotion, cream, ointment)

Stoughton RB. Vasoconstrictor assay—specific applications. In: Maibach HI, Surber C, eds. *Topical Corticosteroids*. Basel, Switzerland: Karger, 1992:42–53.

Evaluation and Management of Food Allergies

In all, 30% to 40% of children with moderate-to-severe AD are affected by one or more food allergies (21); therefore, evaluation for food allergy is warranted in these patients. Offending food allergens may cause allergic reactions that lead to itch/scratch cycle and worsening of AD. The most implicated food allergens are egg, cow's milk, peanut, wheat, and soy. The diagnosis of food allergy in AD patients should be based on a combination of history, skin tests, serum-specific IgE tests, and oral food challenge. Owing to the high risk of developing peanut allergy, moderate-to-severe AD infants have been the subject of the recently published Learning Early About Peanut study (22). The study showed that infants with moderate-to-severe AD who maintained an ingestion of peanut

allergens for the first 5 years have developed significantly less peanut allergy, as compared to those who avoided peanut. Referral of these high-risk infants to allergists for peanut skin tests and oral challenge is recommended (23).

TABLE 29.5 FINGERTIP UNIT (FTU) APPLICATION OF TOPICAL CORTICOSTEROIDS

| | NUMBER OF FTUs | | | | |
| | FACE/NECK | ARM/HAND | LEG/FOOT | TRUNK (FRONT) | BACK/BUTTOCK |
AGE					
3–6 mo	1	1	1.5	1	1.5
1–2 y	1.5	1.5	2	2	3
3–5 y	1.5	2	3	3	3.5
6–10 y	2	2.5	4.5	3.5	5

Long CC, Mills CM, Finlay AY. A practical guide to topical therapy in children. *Br J Dermatol*. 1998;138:293–296.
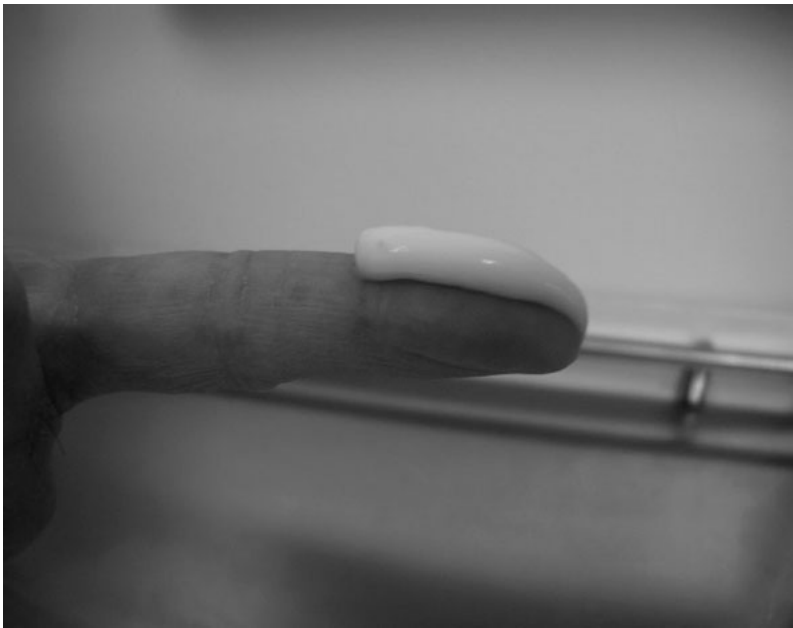
■ **FIGURE 29.2** A fingertip unit is equivalent to the amount of cream/ointment squeezed from a typical tube with 5 mm nozzle onto an adult index finger up to

the distal interphalangeal joint.

The Role of Aeroallergens

There is evidence that direct skin contact with house dust mites (HDMs) or furry animals may exacerbate AD (24). Therefore, HDM control and avoidance of furry animals are recommended in sensitized AD patients. More recently, a double-blind, placebo-controlled study using an environmental challenge chamber showed that direct skin contact with pollens significantly exacerbates eczema in pollen-sensitized AD patients (25). It may be beneficial for pollen-sensitized AD patients to cover their affected areas or areas of potential flare when they are outdoors, especially during pollen season. There is evidence that subcutaneous or sublingual allergen immunotherapy may benefit certain subsets of AD patients. Further studies are needed to confirm these findings.

Management of Infections

More than 95% of AD lesions can be colonized by *S. aureus*. Therefore, routine treatment with antibiotics when there is no sign of infection is not recommended. Signs of skin infections in AD include pain, swelling, mucopurulent discharge, or impetiginous ("honey crusted") lesions. For small, localized areas of skin infections, topical mupirocin should be considered. If the skin infection is widespread, an oral antibiotic such as cephalexin may be given. As methicillin-resistant *S. aureus* is more prevalent in AD patients, a wound culture with antibiotic susceptibility should be considered in cases of treatment failure. Patients who have persistent fever, joint swelling, or focal bone pain should raise the possibility of invasive bacterial infections. Bacteremia is the most common invasive infection in young children with AD. Osteomyelitis and septic arthritis are not uncommon in patients with uncontrolled moderate-to-severe AD. A potential rare invasive infection in severe AD patients is endocarditis. Careful auscultation for heart murmur may be warranted for AD patients with persistent fever. *S. pyogenes* is another common cause of bacterial infections in AD. Routine daily skin care can improve skin barrier functions and decrease the number of bacteria on the skin. Consistent use of TCS on AD lesions decreases inflammation, which is a predisposing factor for bacterial colonization and infection. The use of diluted bleach bath may benefit a subset of patients with recurrent bacterial skin infections. Placebo-controlled studies are needed to evaluate whether diluted bleach bath can improve eczema severity in AD patients without skin infections.

EH is a potentially life-threatening infection in AD. Patients commonly

present with fever and painful vesicular or punched-out rash that superimposes on acute eczematous lesions. Serious complications of EH include viremia, keratoconjunctivitis, and meningitis. On clinical suspicion, oral acyclovir or admission to the hospital for intravenous acyclovir should be initiated. In such cases, viral swab for herpes simplex virus polymerase chain reaction (PCR) should be obtained from the vesicular lesions. In patients with ophthalmic involvement or lesions near the eyes, an urgent ophthalmology consultation should be obtained. For EH patients with disseminated infections, supportive care include intravenous fluids to manage fluid losses, symptomatic management of pain and pruritus, and treatment for secondary bacterial infections.

EC, which is caused by Coxsackie virus, may be confused with EH, because it presents with vesicles. The presence of EC lesions on the buttocks may be a distinguishing feature. In addition, AD patients with EC may present with the typical hand-foot-mouth lesions. A lesional swab for enterovirus PCR may be considered if the diagnosis is still not clear. The management of EC is symptomatic with continuation of routine AD treatments.

EV is caused by live smallpox vaccine (vaccinia virus), which is generally contraindicated in AD patients. EV lesions are characterized by umbilicated pustules and vesicles. Since 911, due to the threat that smallpox virus may be used as a biologic weapon by terrorists, mass vaccinations with smallpox vaccine in military personnel and first responders have been carried out in the United States. With careful screening and exclusion of AD patients from getting this live vaccine, only rare cases of EV have since been reported. However, clinicians should continue to be vigilant of potential EV in this high-risk population and their close contacts.

Other Treatment Options

Topical Calcineurin Inhibitors

Tacrolimus ointment (Protopic, Astellas) 0.03% and pimecrolimus cream (Elidel, Valeant) 1% are approved for children aged 2 years and older with AD, and tacrolimus ointment 0.1% for patients aged 16 years and older. They are both second-line therapies for AD. Tacrolimus ointment is indicated for moderate-to-severe AD and pimecrolimus cream for mild-to-moderate AD. Both products have a Food and Drug Administration (FDA) black box warning of cancer risk. More recent studies have indicated that these medications are safe and effective in children and infants (<2 years) with AD (26,27). These medications are particularly useful for skin atrophy-prone areas, such as the face,

groin, and axillae.

Topical phosphodiesterase 4 inhibitor

Crisaborole is an anti-inflammatory phosphodiesterase 4 (PDE4) inhibitor which has been approved for patients with mild-to-moderate AD aged 2 years and older (28). Its main side effect is a local sting sensation in some patients. It is an non-steroidal alternative, however, post-markerting experience is needed.

Dupilumab

The humanized monocolonal antibody dupilumab blocks the α subunit of IL-4 receptor, which is a common receptor subunit for both IL-4 and IL-13. Dupilumab was shown to decrease the disease severity of AD in Phase 2 and 3 trials (29–31), leading to its approval by FDA in 2017 for adults with moderate-to-severe AD. In the trials, a higher rate of conjunctivitis was noted in the dupilumab-treated group than the placebo group.

Wet-Wrap Therapy

Wet-wrap therapy (WWT) should be considered for acute AD flares in moderate-to-severe AD patients who have failed standard TCS treatment. WWT is done in conjunction with TCS. This therapy improves skin barrier function and intensifies the potency of TCS. The details of WWT procedures have been described in several textbooks and reviews (32). WWT is typically carried out for 5 to 7 days to gain control of severe AD flares. Longer duration or chronic use of WWT is not recommended. Drawbacks of WWT include their labor-intensiveness and potential to increase skin infections. Consultation with a specialist is recommended for WWT.

Systemic Treatments

Recurrent use of systemic corticosteroids is not recommended as a treatment of AD, even in the setting of acute flare. Rebound flares of eczema when patients wean off systemic corticosteroids has been well documented. In addition, the potential side effects of systemic corticosteroids include adrenal suppression, osteoporosis, hypertension, peptic ulcer, glaucoma, cataracts, infections, psychosis, and growth retardation in children. Systemic immunosuppressants, including cyclosporin A, azathioprine, methotrexate, and mycophenolate mofetil, have been used to treat severe AD (33). However, these immunosuppressants are also associated with potential systemic side effects, which must be weighed against the benefit of symptomatic relief. It is also important to note that systemic immunosuppressants further increase the risk of AD patients for EH

and invasive bacterial infection. These medications are generally contraindicated in children. Phototherapy may be effective for some severe AD patients. However, its drawbacks include inconvenience and potential development of skin cancer.

Therapy on the Horizon

Other agents in clinical trials include several high-affinity anti-IgE monoclonal antibodies, Janus kinase inhibitors, anti-IL-22, and anti-TSLP (34).

SUMMARY AND CONCLUSIONS

Significant advances have recently been made in the pathogenesis and treatment of AD. Since the discovery of the important role of IL-4 and IL-13 in AD inflammation (35), the possibility of targeting these cytokines to improve AD has been realized. This is a major step forward in the field of AD, given that there are few safe and effective options for severe AD patients who are adversely affected by psychosocial issues, poor quality of life, and infections. The concept of repairing skin barrier defects in the treatment of AD is appealing. However, postmarketing experience in the use of various prescription barrier creams in the treatment of AD has been disappointing. Nevertheless, the concept of barrier therapy in the prevention of AD is well supported by clinical studies (36,37). These studies showed that early application of skin emollients in neonates at high risk for AD led to a relative risk reduction of up 50% in AD development at 24 to 32 weeks of age, as compared to neonates who did not receive emollients. However, in spite of this success, more than 40% of treated neonates still went on to develop AD at 32 weeks, suggesting that factors other than skin barrier may be important in the pathogenesis of AD or more effective skin barrier creams are needed. Further understanding of mechanisms driving AD will be crucial for more targeted therapy in the prevention and treatment of AD.

ACKNOWLEDGMENTS

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Contact Dermatitis

ANDREW J. SCHEMAN AND KAROLINA ROSZKO

A skin condition commonly encountered by physicians is allergic contact dermatitis. With new chemical sensitizers being introduced into our environment constantly, physicians will be evaluating more instances of this disease. Contact dermatitis is also the most common nontraumatic occupational disease and, as such, is of importance to both the individual and society (1). The patient with allergic contact dermatitis may be very uncomfortable and have poor quality of life. Inability to pursue employment or recreation is common, especially if there is a delay in diagnosis and removal from exposure.

■ IMMUNOLOGIC BASIS

The classification of immunologic hypersensitivity reactions is reviewed in Chapter 17A. Allergic contact dermatitis is a type IVa, T-cell–mediated hypersensitivity. Type IVa allergy is also referred to as delayed-type hypersensitivity, reflecting the fact that typical reactions occur 5 to 25 days after initial exposure and usually 12 to 96 hours after subsequent exposures (although reactions can occur as long as 3 weeks after exposure) (2). In contrast, immediate hypersensitivity is a type I immunoglobulin E (IgE) humoral antibody-mediated reaction, generally occurring within an hour or less.

Whereas the typical skin lesion in immediate hypersensitivity is urticarial, typical allergic contact dermatitis is eczematous (3). Thus, skin lesions can include vesicles, bullae, and poorly demarcated erythematous scaly plaques acutely and, when chronic, lichenification. It is important to realize that contact allergy is often morphologically and histologically identical to other forms of eczema, including atopic dermatitis and irritant contact dermatitis, which is defined as nonimmunologic damage to the skin caused by a direct toxic effect. Therefore, patch testing is usually needed to distinguish contact allergy from other types of eczema.

Typically, immediate hypersensitivity is caused by parenteral exposure

through ingestion or respiratory exposure through inhalation. An exception is immunologic contact urticaria (ICU), in which a type I reaction is induced by topical exposure. The typical type IVa contact allergy is induced by topical exposure. An exception occurs with systemic ingestion of a contact allergen that reproduces skin lesions caused by a previous external exposure to the same or a similar substance; this is termed systemic contact dermatitis (4). The list of substances capable of causing type I allergy is different from the list of substances capable of causing type IVa allergy. There are a few substances, such as penicillin, quinine, sulfonamides, mercury, and arsenic that have can cause both type IVa_1 contact hypersensitivity and type I immediate hypersensitivity reactions.

Although atopic individuals are prone to type I allergies, it is controversial whether they are more likely to develop type IVa allergy than nonatopic individuals (5). On the other hand, it has been clearly demonstrated that atopic persons are much more likely to have a lowered threshold for developing irritant contact dermatitis (6).

Sensitization

The inductive or afferent limb of contact sensitivity begins with the topical application to the skin of a chemically reactive substance called a hapten. The hapten may be organic or inorganic and most commonly of low molecular weight (<500 Da) (3). Its ability to sensitize depends on penetrating the skin and forming covalent bonds with proteins. The degree of sensitization is directly proportional to the stability of the hapten–protein coupling. In the case of the commonly used skin sensitizer dinitrochlorobenzene, the union of the chemical hapten and the tissue protein occurs in the Malpighian layer of the epidermis, with the amino acid sites of lysine and cysteine being most reactive (7). It has been suggested that skin lipids might exert an adjuvant effect comparable with the myoside of *Mycobacterium tuberculosis*.

There is strong evidence that Langerhans cells are of crucial importance in the induction of contact sensitivity (8). These dendritic cells in the epidermis cannot be identified on routine histologic sections of the skin by light microscopy, but they can be easily visualized using special stains. They possess major histocompatibility complex (MHC) class II and B7 homology receptors B7 (CD80/86).

Elicitation

Langerhans cells are dendritic epidermal cells that possess MHC class II antigen on their surface. The Langerhans cell ingests the hapten–protein complex, processes it, and then produces a resulting peptide that binds to the human leukocyte antigen—antigen D related (HLA-DR) on the surface of the cell. The peptide is then presented to a CD4$^+$ helper T-cell type 1 (T$_H$1) with specific complementary surface receptors.

The binding of the T$_H$1 cell induces the Langerhans cell to release cytokines which leads to T-cell proliferation. The proliferating T cells magnify the response by releasing interferon-γ, which leads to increased HLA-DR display on Langerhans cells and increased cytotoxicity of T cells, macrophages, and natural killer cells. The sensitized T$_H$1 cells also result in an anamnestic response to subsequent exposure to the same antigen. Type IVa hypersensitivity can be transferred with sensitized T$_H$1 cells (9).

Contact allergy involves both T effector cells leading to hypersensitivity and T suppressor cells leading to tolerance. The net effect is the balance of these two opposing inputs. Cutaneous exposure tends to induce sensitization, whereas oral or intravenous exposure is more likely to induce tolerance. Once sensitivity is acquired, it usually persists for many years; however, it occasionally may be lost after only a few years. Hardening refers to either a specific or generalized loss of hypersensitivity caused by constant low-grade exposure to an antigen. This type of deliberate desensitization has been successful only in rare instances and is, therefore, not recommended as a therapeutic strategy.

Histopathology

The histologic picture in allergic contact dermatitis reveals that the dermis is infiltrated by mononuclear inflammatory cells, especially about blood vessels and sweat glands (7). The epidermis is hyperplastic with mononuclear cell invasion. Frequently, intraepidermal vesicles form, which may coalesce into large blisters. The vesicles are filled with serous fluid containing granulocytes and mononuclear cells. In Jones–Mote contact sensitivity, in addition to mononuclear phagocyte and lymphocyte accumulation, basophils are found. This is an important distinction from hypersensitivity reactions of the T$_H$1 type, in which basophils are completely absent.

CLINICAL FEATURES

History

Allergic contact dermatitis occurs most frequently in middle-aged and elderly persons, although it may appear at any age. In contrast to the classic atopic diseases, contact dermatitis may be as common in the population at large as in the atopic population, and a history of personal or family atopy has not been proven to be a risk factor (5).

The interval between exposure to the responsible agent and the occurrence of clinical manifestations in a sensitized subject is usually 12 to 96 hours, although it may be as early as 4 hours and as late as 3 weeks (2). The incubation or sensitization period between initial exposure and the development of skin sensitivity may be as short as 2 to 3 days in the case of a strong sensitizer such as poison ivy, or several years for a weak sensitizer such as chromate. The patient commonly will note the development of erythema, followed by papules, and then vesicles. Pruritus follows the appearance of the dermatitis and is uniformly present in allergic contact dermatitis.

Physical Examination

The appearance of allergic contact dermatitis depends on the stage at which the patient presents. In the acute stage, erythema, papules, and vesicles predominate, with edema and occasionally bullae (Fig. 30.1). The boundaries of the dermatitis are generally poorly marginated. Edema may be profound in areas of loose tissue, such as the eyelids and genitalia. Acute allergic contact dermatitis of the face may result in a marked degree of periorbital swelling that resembles angioedema. The presence of the associated dermatitis should allow the physician to make the distinction easily. In the subacute phase, vesicles are less pronounced, and crusting, scaling, and early signs of lichenification may be present. In the chronic stage, few papulovesicular lesions are evident, and thickening, lichenification, and scaliness predominate.

■ FIGURE 30.1 The acute phase of contact dermatitis as a result of poison ivy. Note the linear distribution of vesicles. (Courtesy of Dr Gary Vicik.)

Different areas of the skin vary in their ease of sensitization. Pressure, friction, and perspiration are factors that seem to enhance sensitization. The eyelids, neck, and genitalia are among the most readily sensitized areas, whereas the palms, soles, and scalp are somewhat more resistant. Tissue that is irritated, inflamed, eroded, or infected is more susceptible to allergic contact dermatitis. A clinical example is the common occurrence of contact dermatitis in an area of stasis dermatitis that has been treated with topical medications or sensitizing chemicals.

Differential Diagnosis

The skin conditions most frequently confused with allergic contact dermatitis are seborrheic dermatitis, atopic dermatitis, psoriasis, primary irritant dermatitis, and rosacea. In seborrheic dermatitis, there is a general tendency toward oiliness of the skin, and a predilection of the lesions for the scalp, the T-zone of the face, midchest, and inguinal folds. In rosacea, the T-zone of the face and sometimes periocular skin is commonly involved.

Atopic dermatitis (see Chapter 29) often has its onset in infancy or early childhood. The skin is dry, although pruritus is a prominent feature; it appears before the lesions and not after them, as in the case of allergic contact dermatitis. The areas most frequently involved in adults and older children are the flexural surfaces, but atopic eczema can occur anywhere on the body. The margins of the dermatitis are indefinite, and the progression from erythema to papules to vesicles is not seen.

Psoriatic dermatitis is characterized by well-demarcated erythematous plaques

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with white to silvery scales, pruritus is often mild or absent. Lesions can occur anywhere but are often distributed symmetrically over extensor surfaces, such as the knee or elbow.

The dermatitis caused by a primary irritant is a simple chemical or physical insult to the skin. For example, what is commonly called "dishpan hands" is a dermatitis caused by household detergents. A prior sensitizing exposure to the primary irritant is not necessary, the dermatitis develops in a large number of normal persons; however, atopic patients are especially susceptible (6). The dermatitis begins shortly after exposure to the irritant, in contrast to the 12 to 96 hours after exposure to in allergic contact dermatitis. Primary irritant dermatitis may be virtually indistinguishable in its physical appearance from allergic contact dermatitis. It should be emphasized that skin conditions may coexist. It is not unusual to see allergic contact dermatitis caused by topical medications applied for the treatment of atopic dermatitis and other dermatoses.

A variant of contact allergy is contact urticarial (CU). There are three categories of CU: immunologic contact urticaria (ICU), protein contact dermatitis (PCD), and nonimmunologic contact urticaria (NCU). ICU is an immediate wheal-and-flare response generated by a wide variety of contactants. The immunopathogenesis of both ICU and PCD appears to be mediated at least in part by antigen-specific IgE and type I hypersensitivity. The immunopathologic mechanisms in PCD other than type I are unclear. Several authors have reported type IV cutaneous reactions, corroborated by positive patch tests (10). NCU is caused by some allergens, such as fragrances and benzyl alcohol, known to cause immunologic reaction; however, in the case of NCU, the etiology is unclear.

IDENTIFYING THE OFFENDING AGENT

History and Physical Examination

Once the diagnosis of allergic contact dermatitis is made, vigorous efforts should be directed toward determining the cause. A careful, thorough history is absolutely mandatory. The temporal relationship between exposure and clinical manifestations must be kept in mind because an exhaustive search is made for exposure to a sensitizing allergen in the patient's occupational, home, or recreational environment. The location of the dermatitis most often relates closely to direct contact with a particular allergen. At times, this is rather straightforward, such as dermatitis of the feet, caused by contact sensitivity to shoe materials or dermatitis from jewelry appearing on the wrist, the ear lobes,

or the neck. The relationship of the dermatitis to the direct contact allergen may not be as obvious at other times, and being able to associate certain areas of involvement with particular types of exposure is extremely helpful. Contact dermatitis of the face, for example, is often caused by cosmetics directly applied to the area. One must keep in mind other possibilities, however, such as hair dye, shampoo, hair-styling preparations, and allergens passively transferred from the hands. Contact dermatitis of the eyelid, although often caused by eye shadow, mascara, and eye liner, may also be caused by nail polish or nickel transferred from the hands. Involvement of the thighs may be caused by keys or coins in pants pockets. Therefore, it is vital that the physician be familiar with various distribution patterns of contact dermatitis that may occur in association with particular allergens.

Frequently, the distribution of the skin lesions may suggest a number of possible sensitizing agents, and patch testing is of special value. Certain allergens may be airborne, and exposure may occur by this route. Airborne contact allergy to composite plants is common. Dermatitis among farmers caused by ragweed oil sensitivity occurs occasionally. Smoke from burning the poison ivy plant may contain the oleoresin as particulate matter, and thus expose the sensitive individual. Forest firefighters develop generalize allergic contact dermatitis from smoke from the burning branches and leaves containing urushiol. Another route of acquiring poison ivy contact dermatitis without touching the plant is by indirect contact with clothing or animal fur containing the oleoresin. It should be remembered also that systemic administration of a drug or a related drug that has been previously used topically and to which the patient has been sensitized can elicit a localized or generalized eruption. An example is sensitivity to ethylenediamine. A patient may have developed localized contact dermatitis to topically applied ethylenediamine hydrochloride previously used as a stabilizer in compounds, such as Mycolog cream. After being sensitized, a localized or generalized eruption may then occur when aminophylline (which contains ethylenediamine) or hydroxyzine (which is based on a dimer of ethylenediamine) is administered orally (11).

The oral mucosa may also be the site of a localized allergic contact reaction, resulting in contact stomatitis or stomatitis venenata (12). The relatively low incidence of contact stomatitis compared with contact dermatitis is attributed to the brief duration of surface contact, the diluting and buffering action of saliva, and the rapid dispersal and absorption because of extensive vascularity. Agents capable of producing contact stomatitis include dentifrices, mouthwashes, dental materials such as acrylic and epoxy resins, and foods. The clinical response is

most commonly inflammation of the lips, but cases of "burning mouth" syndrome have infrequently been attributed to contact allergy.

Patch Testing

Principle

Patch testing or epicutaneous testing is the diagnostic technique of applying a specific substance to the skin with the intention of producing a small area of allergic contact dermatitis. It can be thought of as reproducing the disease in miniature. The patch test is generally kept in place for 48 hours (although reactions may occasionally appear after only 24 hours) and then observed for the appearance of a localized dermatitis (most commonly after 48 and 96 hours). The same principles of proper interpretation of a positive patch test are applied as in the case of the immediate wheal and erythema skin test reaction (see Chapter 8). A positive patch test is not absolute proof that the test substance is the actual cause of dermatitis. It may reflect a previous episode of dermatitis, or it may be without any clinical relevance at all. The positive patch test must always correlate with the patient's history and physical examination.

Allergic Contact Dermatitis and Indications for Patch Testing

All unexplained cases of eczema that either do not respond to treatment or recur after treatment may be because of contact allergy and should be considered for patch testing (13). Currently, patch testing is the only accepted scientific proof of contact allergy. If patch testing is successful at identifying a causative allergen, avoidance often will be curative. Alternatively, if the causative agent is not identified, it is likely that the patient will need ongoing treatment and that treatment will be less than optimal.

A thorough history and physical examination should be performed with emphasis on the distribution and timing of the clinical lesions. Once this information is obtained, an exhaustive history should be taken to identify all potential allergens that had opportunity to come in contact with the skin of the patient. A tray of patch test materials is then assembled.

Most physicians doing patch testing use the TRUE Test, a readymade series of 35 common allergens that can be easily applied in a busy office setting (Table 30.1). Because a 2012 study reported that less than 28% of contact allergy problems will be fully solved using the 25-item TRUE Test, patients often need referral to a physician specializing in patch testing (14). Although the TRUE Test now contains 35 allergens, it still likely picks up a minority of contact

allergy. These specialists will generally have a wide array of allergens relevant to most occupations and exposures and are familiar with where these allergens are found and alternatives to avoid exposure. Testing is usually performed with an expanded standard tray and additional allergens individualized to the patient exposure.

The physician should become familiar with potent sensitizers and with the various modes of exposure. It is important to keep in mind the possibility of cross-reactivity to other allergens because of chemical similarities. Sensitivity to paraphenylenediamine (PPD), for example, may also indicate sensitivity to para-aminobenzoic acid (PABA) and other chemicals containing a benzene ring with an amino group in the "*para*" position.

The most common cause of type IVa-delayed hypersensitivity allergic contact dermatitis in the United States is *Toxicodendron* (poison ivy, poison oak, poison sumac). In contrast, latex-induced contact dermatitis is a type I contact urticaria that affects health care workers, patients with spina bifida, and manufacturing employees who prepare latex-based products. Table 30.2 is a list of the top 20 allergens in the United States as reported by the North American Contact Dermatitis Group (15). More detailed information on other sensitizers, environmental exposures, and preparation of testing material is contained in several standard references, including the 2015 practice parameter update on contact dermatitis (16–18).

Techniques

The two most common types of patch test chambers, the aluminum Finn chamber and the plastic IQ chamber, come in strips that hold 10 allergens (13). Allergens are placed into the chambers as a drop of liquid on filter paper or in petrolatum from a syringe.

With the patient standing erect, the patch test strips are applied starting at the bottom and pressing each allergen chamber firmly against the skin as it is applied. The skin surrounding the patch test strips is then outlined with either fluorescent ink or gentian violet marker. Reinforcing tape, and sometimes a medical adhesive such as Mastisol, is then used to further affix the patches in place. The patch test series is documented in the medical records clearly showing the position of each allergen. The patient should be instructed to keep the patch test sites dry and avoid vigorous physical activity until after patch test reading is completed. The allergens are removed and read 48 hours after application, and the patient returns for a second reading of the patch tests commonly at 72 or 96 hours. A 96-hour reading picks up more positive reactions than a final reading at

72 hours (19). Some physicians also do readings at 1 week after application to identify more delayed reactions.

TABLE 30.1 ALLERGENS ON THE 2016 TRUE TEST PANELS LISTED BY FUNCTION

Metals	Nickel sulfate, potassium dichromate, cobalt chloride, gold sodium thiosulfate
Medications	Caine mix, neomycin sulfate, bacitracin, ethylenediamine dihydrochloride, quinolone mix, hydrocortisone-17-butyrate, tixocortolpivalate, budesonide
Cosmetic fragrances	Fragrance mix, Balsam of Peru
Cosmetic preservatives	Paraben mix, quaternium-15, Kathon CG, formaldehyde, methyldibromoglutaronitrile, thiomersal, diazolidinylurea, imidazolidinylurea, Bronopol
Other cosmetic ingredients	Colophony (rosin), paraphenylenediamine, lanolin (wool wax) alcohol
Rubber ingredients	Mercaptobenozothiazole, mercapto mix, carba mix (carbamates), thiuram mix, black rubber paraphenylenediamine mix
Adhesives	Epoxy resin, paratertiary butylphenol formaldehyde resin
Textile dyes	Disperse blue 106
Plant allergens	Parthenolide

TABLE 30.2 THE 20 MOST COMMON ALLERGENS IN THE UNITED STATES (15)

1450

Nickel sulfate hexahydrate 2.5% pet.

Fragrance mix 8.0% pet.

Neomycin sulfate 20.0% pet.

Myroxylon pereirae resin (Balsam of Peru) 25.0% pet.

Bacitracin 20.0% pet.

Cobalt(II) chloride hexahydrate 1.0% pet.

Formaldehyde 1.0% aq.

Quaternium-15 2.0% pet.

4-Phenylenediamine base 1.0% pet.

Fragrance mix II 14.0% pet.

Methylchloroisothiazolinone/methylisothiazolinone 0.01% aq.

Carba mix 3.0% pet.

Lanolin alcohol (Amerchol L-101) 50% pet.

Iodopropynylbutylcarbamate 0.5% pet.

Cinnamal (cinnamic aldehyde) 1.0% pet.

Methyldibromoglutaronitrile/phenoxyethanol 2.0% pet.

Carmine 2.5% pet.

Thiuram mix 1.0% pet.

Propylene glycol 30.0% aq.

Tixocortol-21-pivalate 1.0% pet.

Aq, aqueous; pet, petrolatum.

It is essential that the skin of the back be free of eczema at the time of testing to avoid false-positive reactions due to what has been called the "angry back syndrome." It is also important that the testing site has not been exposed to topical steroids the preceding week or ultraviolet light during the preceding month. Oral steroids should be avoided when possible; however, some strong patch test reactions can be obtained even when a patient is taking up to 20 mg prednisone daily (20).

Photoallergy and Photopatch Testing

When an eruption is observed in a sun-exposed distribution, photoallergic contact dermatitis should be considered. Photoallergy is identical to allergic

contact dermatitis with the exception that the allergen in contact with the skin must be exposed to ultraviolet A (UVA) light for the reaction to occur. Photopatch testing is performed similar to routine patch testing, but a second identical set of allergens is also applied to the back. Approximately 48 hours after application, one set of allergens is uncovered and exposed to 10 J of UVA light. These patches are then carefully reapplied and removed at 72 hours. Both sets of tests are then read at 96 hours. A photoallergy is confirmed if only the site exposed to UVA light shows a reaction. If both the exposed and unexposed sites show equal reactions, a standard contact allergy is confirmed. A stronger reaction at the site exposed to UVA indicates contact allergy augmented by coexisting photoallergy.

Patch Testing Reading and Interpretation

The patch tests are read using a template that is aligned inside the marker lines on the back to show the exact position of each allergen. The sites are then graded as 1+ (erythema), 2+ (edema or vesiculation <50% of the patch test site), 3+ (edema or vesiculation >50% of the patch test site), ± or ? (questionable), or Ir (irritant). Strong irritant reactions sometimes result in a sharply demarcated, shiny, eroded patch test site. Weak irritant and allergic reactions are often morphologically indistinguishable.

One of the most important aspects of patch testing is to determine whether patch test reactions are relevant to the patient's clinical condition. Some patch test reactions merely indicate sensitization from an exposure that occurred many years prior. In addition, false-positive reactions are not uncommon. Pustular patch test reactions can occur with metal salts and do not indicate contact allergy. Some allergens, such as nickel, glutaraldehyde, and potassium dichromate, are tested at levels that can also cause an irritant reaction. In addition, when a test site is strongly positive or if the patient experiences severe irritation from tape, nearby sites may show false-positive reactions due to the "angry back syndrome." When in doubt, a "use test" can be performed by applying a suspected substance twice daily for 2 weeks to the antecubital fossa to confirm or exclude an allergic reaction.

Reactions to Cosmetics and Skin Care Products

Although most skin care products available are quite safe, allergic reactions can occur occasionally to almost any cosmetic product. The most common causative agents are fragrance and preservative ingredients. A discussion of some common cosmetic allergens follows.

Fragrance

Fragrance is found in a wide variety of cosmetic products and is the most common cause of cosmetic allergy. It is responsible for a relatively large number of allergic reactions to cosmetics (21–23). This is partially because fragrance is not a single ingredient but is, instead, a general name that includes a variety of individual fragrance ingredients. Individual ingredients in fragrance are usually not listed on product labels in the United States, whereas products sold in Europe are required to list 26 of the most common fragrance ingredients (EUF) on product labels. It is important to read the actual ingredient list on products and avoid products that contain fragrance, perfume, or essential oils. Essential oils (i.e., cinnamon oil, clove oil, rosewood oil) are often used as fragrance ingredients, and at least 31 are proven contact allergens (24). Labels that claim that the product is "unscented" or "fragrance free" can be misleading. Unscented products may contain a masking fragrance designed to eliminate odors, and fragrance-free products can sometimes include essential oils that the manufacturer may not consider as fragrance. Also, consumers should beware of other less obvious fragrance ingredients that may be listed on the label, such as benzyl alcohol.

There are two materials in the TRUE test, patch test tray, that screen for allergy to fragrance. Fragrance mix I is a mixture of eight common fragrance ingredients, and three decades ago, it was reported to be able to identify about 80% of individuals allergic to fragrance (25). Balsam of Peru is an extract from a tree in the *Myroxylon* genus; it contains many constituents used commonly in fragrances and was originally thought to identify 50% of fragrance-allergic patients (25). In the mid-1990s, it was believed that these two screening substances, fragrance mix and Balsam of Peru, together would identify over 90% of all fragrance allergy (26). Balsam of Peru is used in the artificial flavoring industry, and individuals allergic to the substance may have reactions to sweet junk foods, condiments, mouthwashes, toothpaste, cough medicines, liqueurs, and spiced teas. It can also cross-react with citrus peels and tomatoes. It is rarely used directly in the fragrance industry (27). Because newer fragrance ingredients have been introduced into the fragrance industry, these screening ingredients only identified 57.6% of patients who reacted to one or more of the EUF tested individuals in one study. Therefore, the use of Balsam of Peru and both fragrance mixes I and II now appears to miss a substantial number of patients allergic to fragrance (28).

Formaldehyde-Releasing Preservatives

Formaldehyde is still the most effective cosmetic preservative against Gram-negative bacteria. Substances that release formaldehyde are therefore still commonly used in skin care and cosmetic products (29). Currently used formaldehyde-releasing preservatives include quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, and 2-bromo-2-nitropropane-1,3-diol (Bronopol). Individuals allergic to one of these ingredients may cross-react to any of the other formaldehyde-releasing preservatives. Therefore, it is often good advice to avoid all of these substances if patch testing results to one of them are clearly positive.

Parabens

Parabens are the most commonly used preservatives in facial cosmetics and are relatively infrequent sensitizers. A person who has an allergic reaction to parabens may still be able to use paraben-containing products if they are only applied to undamaged skin. That is, almost all paraben allergic reactions occur on inflamed or cracked skin; this has been termed the paraben paradox (30).

Parabens are also found in syrups, milk products, soft drinks, candies, jellies, and some systemic medications. However, no sensitization has been reported by ingestion of parabens. Foods containing various preservatives that are known to be topical contact allergens have been occasional causes of hand dermatitis in cooks and bakers.

Kathon CG

Kathon CG (methylisothiazolinone and methylchloroisothiazolinone) is a preservative system that has become a common sensitizer (31). The regulations in the United States on use of methylisothiazolinone in topical products now allow higher concentrations of this preservative, and there has been a significant increase in patients allergic to this allergen (15). In addition to being used in skin, hair, and cosmetic products, it is found in oils and cutting fluids used by machinists and in latex paint.

Methyldibromoglutaronitrile

Methyldibromoglutaronitrile is a preservative that frequently causes contact allergy (32). It has not achieved a strong market presence in the United States and is being used less frequently now that it has been identified as a frequent sensitizer.

Iodopropynyl Butylcarbamate

Iodopropynyl butylcarbamate is a preservative used in skin care and cosmetic

products which has been an occasional cause of contact allergy (33). It is also used as an antifungal agent in paints.

Sorbic Acid

Sorbic acid is another cosmetic preservative that only occasionally causes allergic reactions (34). Persons allergic to sorbic acid may also react to potassium sorbate. Sorbic acid can also cause NCU.

Thimerosal

Thimerosal is primarily found in vaccines and liquid products for use in the eyes, nose, and ears (35). Aside from its use in vaccines, it is now used only in occasional products and is now rarely a relevant contact allergen. Reactions to its use in vaccines are usually injection site reactions and are not common (36).

Benzocaine and Caine Mix

Benzocaine cross-reacts with other benzoate ester anesthetics, such as procaine, tetracaine, and cocaine (35). It may also cross-react with other para compounds, such as *para*-aminosalicylic acid, PABA, PPD, procainamide, and sulfonamides. Cross-reaction with amide anesthetics, such as lidocaine, dibucaine, mepivacaine, and cyclomethycaine, is uncommon.

Paraphenylenediamine

Another well-recognized contact sensitizer, PPD, is an ingredient in permanent, demipermanent, and semipermanent hair dyes (37). This ingredient can be avoided by use of certain temporary hair dyes, metallic hair dyes, henna, or occasional other dye products without PPD. Some patients allergic to PPD can tolerate newer PPD-free salon dyes containing *para*-toluenediamine sulfate; however, they must first patch test negative to this allergen and other common hair dye allergens (38). Persons allergic to this ingredient may also react to similar "para compounds" such as PABA and its derivatives (found in sunscreens), benzocaine (found in skin anesthetics such as sunburn medications), procaine, sulfonamides, *para*-aminosalicylic acid, and azo dyes (in synthetic clothing fabrics). Allergy to hair dye can be problematic for hair colorists because PPD penetrates readily through latex gloves.

Glyceryl Thioglycolate

Glyceryl thioglycolate is found in the acid permanent wave products used in salons (37). This is a common cause of contact allergy in hairdressers because it can permeate latex gloves. Alkaline permanent waves predominate in retail stores and are also commonly used in salons. These products contain ammonium

thioglycolate, which rarely cross-reacts with glyceryl thioglycolate.

Lanolin

Lanolin is a moisturizing substance obtained from the sebaceous secretions of sheep (39). The alcohol fraction of lanolin is the most common sensitizing portion. Individuals allergic to lanolin need to also avoid products displaying the European names such as wool wax and wool wax alcohol (synonymous with lanolin and lanolin alcohol, respectively) and other lanolin derivatives.

Propylene Glycol

Propylene glycol is a versatile ingredient that is both a solvent and a humectant (40). It can be an irritant that stings when applied to inflamed or cracked skin, and can also cause true allergic reactions.

Toluene Sulfonamide/Formaldehyde Resin

Toluene sulfonamide/formaldehyde resin is found in nail polish and is a common cause of eyelid contact allergy (41). Nail polishes containing other resins in place of this ingredient can be used by persons who are allergic to toluene sulfonamide/formaldehyde resin.

Cocamidopropyl Betaine

There have been a number of reports of contact allergy to cocamidopropyl betaine (CPB) (42). This ingredient is used in baby shampoos because of its gentleness and also because it does not sting when it gets onto the eyes. It is now used more widely in many types of shampoos and cleansers. The sensitizers appear to be impurities formed in the manufacture of the ingredient (dimethylaminopropylamine and amidoamine), and patch testing to these chemicals will often identify individuals allergic to CPB (42).

Sunscreen Ingredients

Sunscreen ingredients that can cause allergic reactions include PABA and its derivatives, benzophenone, octocrylene, and Parsol 1789 (also called avobenzone or butylmethoxydibenzoylmethane) (43). These sunscreen ingredients are also found in many other cosmetic products, including foundations, pressed powders, antiaging products, lip and nail products, and toners.

One cause of sunscreen allergy is PABA and its derivatives. The derivatives of PABA include glyceryl PABA and octyl dimethyl PABA (also called Padimate O). Unfortunately, there are products on the market that claim to be

PABA free but which include PABA derivatives. PABA and its derivatives are being used much less commonly in products available currently.

The benzophenones, especially oxybenzone, are now the most common cause of contact allergy to sunscreens. Parsol 1789 (avobenzone) and octocrylene are newer sunscreens that can cause both contact allergy and photoallergy (43,44). Cinnamates are occasional photosensitizers. Salicylates rarely have also caused contact allergy.

Colophony (Rosin)

Colophony or rosin is derived from the sticky sap of pine trees or other conifers (45). It is used in some cosmetics, adhesives (commonly in shoe adhesives), tape, flypaper, epilating wax, rosin for athletics and violinists, furniture polish, adhesives, recycled paper, and waxes for cars or floors. Colophony cross-reacts with derivatives, such as abietic acid, abitol, and dihydroabietic acid, which are also used in cosmetic products.

Medications That Are Sensitizers

A number of medications have been reported to cause allergic contact dermatitis. In the case of topical medications, it is important to consider vehicle ingredients as possible contact allergens in addition to the active drug.

Topical Steroids

It is now appreciated that topical steroids are a fairly frequent cause of contact allergy (46,47). The medical literature divides topical steroids into five structural groups. The American Contact Dermatitis Core Series recommends the following screening allergens for each group: group A (tixocortol pivalate), group B (budesonide), group C (desoximetasone), group D_1 (clobetasol-17-propionate), and group D_2 (hydrocortisone-17-butyrate) (45). Cross-reactions between structural groups occur fairly commonly. More recent data suggests that C_{16} methylated steroids (groups C and D_1) tend to cause less contact allergy (48).

Ethylenediamine and Related Drugs

Ethylenediamine was most commonly found in Mycolog cream, but is not in the current Mycolog II. It is now found rarely in a small number of topical products. Systemic contact allergy can occur in individuals who have contact allergy to ethylenediamine after administration of aminophylline (which contains 33% ethylenediamine by weight as a stabilizer), piperazine antihistamines (such as

hydroxyzine and cetirizine), ethylenediamine-related motion sickness medications and menstrual analgesics (49).

Neomycin and Bacitracin

Bacitracin and neomycin often cause contact allergy because they are used on injured skin with damaged barrier function (50). Neomycin may cross-react with gentamycin, tobramycin, and other aminoglycosides. Bacitracin is recognized to be a frequent cause of contact allergy. Many patients are allergic to both neomycin and bacitracin. This probably does not represent a true cross-reaction but rather reflects co-reaction owing to the fact that these two ingredients are often in the same products.

Quinolones

Quinolones are antimicrobial medications that can occasionally be sensitizers (51). 8-Hydroxyquinolone is found in Bag Balm. Iodoquinol and iodochlorhydroxyquin are found in some prescription topical medications.

Mercurials

Mercurials are divided into organics or inorganics (52). Organics include Merthiolate (thimerosal) and Mercurochrome (merbromin). Inorganics found today include mercury (older style thermometers) and phenylmercuric acetate (an occasional preservative in eye solutions). Cross-reactions can occur between organic and inorganic mercury substances. Thimerosal exposure is now rare because it is found only in a few topical eye, ear, and nasal medications and some vaccines (the latter that can rarely cause injection site reactions) (36).

Metals

Metals can cause both allergic and irritant contact dermatitis. Moisture under jewelry from repeated handwashing is a common cause of irritant dermatitis to metals. The most common cause of skin discoloration to metals is because of the abrasive action of powders in cosmetic products on metal jewelry. The resulting black powder produces what has been called black dermatographism which is not an allergic reaction.

Nickel

Nickel is the most common cause of allergic contact dermatitis in patients undergoing patch testing (53). Sensitization often occurs via ear or body piercing. Metal jewelry that contains a significant amount of nickel can be identified using a dimethylglyoxime nickel test kit. Some alloys of steel can cause nickel contact allergy; however, the nickel in stainless steel is so often

firmly bound that reactions may only occur with prolonged contact and sweat.

A significant amount of nickel is not only found in jewelry but also in keys, blue jean buttons, bobby pins, safety pins, some coins, eyeglass frames, zippers, bra and garter snaps, door knobs, scissors, pens, and shoelace eyelets. Nickel is also used in many alloys of chrome and white gold.

Chromium

Chromium causes both allergic and irritant reactions; however, allergic reactions are more common (53). Allergy to chrome or chrome-plated objects is uncommon. When reactions to chrome products occur, the reaction is usually because of nickel in the product.

Most allergic reactions to chromium are to hexavalent chromates in tanned leather or cement. Chromates are the most common cause of contact allergy to leather and are used in soft tanned leather of the type commonly found on shoe uppers. Potassium dichromate is also found in Portland cement and green tattoos. Chromate reactions in cement workers are often severe, chronic, and may persist many years after exposure to cement has ended.

Cobalt

Cobalt is found in some costume jewelry alloys, blue eye shadow, and some blue art materials and is used to tan fine leather (similar to potassium dichromate) (54). Occupational exposure includes masons, construction workers, tile workers, dentists, printers, mechanics, and machinists.

Gold

Gold was the sixth most common contact allergen reported by the North American Contact Dermatitis Group in 2003 to 2004 (the last years gold was included in their data) (55). However, many individuals who test positive to gold will tolerate gold jewelry. Contact allergy to gold often occurs on the face rather than at the site where gold jewelry is worn (56).

Tattoos

Several metals used in tattoos can cause allergic contact dermatitis: red tattoos may contain mercury sulfide (red cinnabar); green tattoos may contain chromium oxide; blue tattoos may contain cobalt aluminate; and yellow tattoos may contain cadmium yellow (a possible cause of phototoxic reactions) (57). However, the tattoo industry is increasingly moving toward nonmetallic organic pigments (58).

Rubber-Related Compounds

Latex products can cause type I allergy as well as type IVa allergy (59). Type I latex allergy to gloves may present as a localized contact urticaria that can mimic an allergic contact dermatitis. Alternatively, latex protein can be inhaled on particles of powder from gloves and cause widespread urticaria and anaphylaxis. *In vitro* testing can be used to screen for type I allergy to latex but does not have 100% sensitivity. Therefore, the skin-prick test is still the gold standard for type I latex allergy testing. Unfortunately, no US Food and Drug Administration-approved latex extract is available yet in the United States for skin-prick testing.

Alternatively, chemicals used to process rubber frequently cause type IVa allergy to both latex products and artificial rubber (nitrile rubber). Mercapto compounds, thiurams and carbamates, are rubber accelerators that can cause allergic contact dermatitis. Thiurams and carbamates are also used in insecticides and fungicides and are often found on lawns and garden plants. Disulfiram (a thiuram) is also the active ingredient in Antabuse. Carbamates are rubber accelerators that are closely related to thiurams and cross-reactions are common. Currently, carbamates are the most common accelerators used in latex, nitrile, and many medical gloves.

Black rubber PPD is an antioxidant used in the manufacture of black rubber. This is a relatively uncommon sensitizer because contact with black rubber is not frequent for most individuals. Thioureas are accelerators used mostly in neoprene and are less common cause of allergy.

Clothing-Related Dermatitis

Most clothing fibers are nonsensitizers or rare sensitizers (60). Dyes used in clothing and athletic shoes can cause allergic reactions (61). The disperse dyes, such as azo and anthraquinone dyes, which are used on synthetic fabrics, are most problematic. Some persons reacting to azo dyes cross-react with PPD, PABA, and other "para" compounds.

Fabrics-containing cotton or rayon no longer usually contain formaldehyde resins that release a significant small amount of free formaldehyde (62). Allergy to free formaldehyde has become less common because manufacturers have reduced the levels of free formaldehyde in fabrics. Nevertheless, it is still possible to have contact allergy to the formaldehyde resins used in these fabrics (especially in uniforms and upholstery). These individuals may or may not cross-react to formaldehyde.

Because allergy to clothing is frequently not identified using a standard patch test, testing often requires specialized nonstandard allergens. Other causes of

clothing dermatitis include reactions to rubber used in elastic. Spandex (except some from Europe which contains mercaptobenzothiazole) and Lycra are good substitutes.

Plastic-Related Dermatitis

Plastics that can sensitize include epoxies, paratertiary butylphenol formaldehyde resin (commonly used as a leather adhesive), and acrylate and methacrylate monomers (63,64).

Acrylate and methacrylate monomers, used in dental bonding procedures, are a common cause of contact allergy in dentists and their patients. These allergens can penetrate rubber gloves. If the material fully polymerizes and hardens, it is no longer allergenic. Acrylic, gel nails, no-chip nail products, and acrylic prostheses can also cause sensitization. Cyanoacrylate adhesives (superglue products and liquid bandages) also cause contact allergy (65).

Plants

Allergic contact dermatitis to plants is most commonly because of the oleoresin fraction, especially the essential oil fraction. In contrast, type I reactions to plants are most commonly caused by pollen and other plant proteins.

Toxicodendron (Rhus)

Toxicodendron dermatitis (poison ivy, oak, and sumac) is the most common form of allergic contact dermatitis seen in both children and adults in the United States (66,67). Previously called rhus dermatitis, these plants have been reclassified as toxicodendron. Cross-reactions can occur with other Anacardiaceae, such as Japanese lacquer tree, marking nut tree of India, cashew nutshells, mango, Ginkgo tree fruit pulp, and the Rengas (black varnish) tree.

Ragweed

Ragweed dermatitis generally affects older individuals and rarely occurs in children (68). Men are affected 20 times more often than women. Affected persons are not usually atopic. The allergic contact reaction is a type IVa hypersensitivity to the oil-soluble fraction. Type I reactions to the protein fraction lead to allergic rhinitis. Contact allergy typically occurs in early fall. A rash involving exposed areas may develop from airborne ragweed exposure.

Compositae

Compositae are ubiquitous in many parts of the world (68). This large family of

around 1,200 plants includes parthenium, chrysanthemums, daisies, asters, arnica, artichokes, burdock, chamomile, chicory, cocklebur, feverfew, lettuce, marigold, marsh elder, pyrethrum, ragweed, sagebrush, sunflower, tansy, and yarrow. The sensitizers in these plants are sesquiterpene lactones. Although sesquiterpene lactone and compositae mixes are available for patch testing and will be positive in many cases of compositae allergy; it will miss some cases because different sesquiterpene lactones are found in various compositae plants.

Alstromeria

Alstromeria (Peruvian lily) is the most common cause of contact allergy in florists and is owing to tuliposide-A (α-butyrolactone) (69). Cross-reactions may occur from handling tulip bulbs.

Photoreactions

Phototoxic reactions are because of nonimmunologic mechanisms, usually occur on first exposure, and tend to resemble sunburn (70). The action spectrum of two common causes, coal tar and psoralens, is primarily UVA.

Phytophotodermatitis

Phytophotodermatitis is a phototoxic reaction to UVA light caused by furocoumarins in several families of plants, especially Umbelliferae (71). The Umbelliferae family includes carrots, celery, parsnips, fennel, dill, parsley, caraway, anise, coriander, and angelica. Also, Rutaceae plants (orange, lemon, grapefruit, lime, and bergamot lime) are possible causes. Phototoxic dermatitis on the neck is sometimes caused by perfumes containing oil of bergamot (bergapten or 5-methoxy-psoralens). Bartenders handling Persian limes can also develop phytophotodermatitis.

Photoallergic Contact Reactions

Type IVa hypersensitivity mediates photoallergic contact reactions (72). The most common cause in the past was halogenated salicylanilides in soaps and cleansers; however, these are no longer used in the United States or Europe. Hexachlorophene, a halogenated phenol, can also cause photoallergy and can cross-react with these compounds.

Today, sunscreen ingredients, such as octocrylene, PABA, benzophenones, cinnamates, and avobenzone, are common causes of photoallergy. Fragrances are another common cause.

Phenothiazines are used in insecticides and can cause topical photoallergy and

phototoxic reactions. This does not occur by the oral route, with the exception of chlorpromazine, which can cause phototoxic reactions.

Most topical sulfonamides are not photosensitizers, but sulfanilamide can cause both photoallergic and phototoxic reactions. Oral sulfonamides, tetracyclines, fluoroquinolones, hypoglycemics, and thiazides can cause both photoallergic and phototoxic reactions.

Precautions

Several precautions must be observed in patch testing. The application of the test material itself may in very rare cases sensitize the patient. Potent materials that may sensitize on the first application include plant oleoresins and PPD. Patch testing and, especially, repeated patch testing should not be performed unnecessarily. In testing, one has to avoid provoking nonspecific inflammation. The testing material must be dilute enough to avoid a primary irritant effect. This is especially important when testing with an allergen not included in the standard patch test materials. To be significant, a substance must elicit a reaction at a concentration that will not cause reactivity in a suitable number of normal controls. Patch testing should ideally not be performed in the presence of an acute or widespread contact dermatitis because false-positive reactions may be obtained because of increased reactivity of the skin. In addition, a positive patch test reaction with the offending agent may cause a flare-up of the dermatitis. As mentioned earlier, an anaphylactic reaction can occur when testing for ICU.

■ COMPLICATIONS

The most common complication of allergic contact dermatitis is secondary infection caused by the intense pruritus and subsequent scratching. An interesting but poorly understood complication is the occasional occurrence of the nephrotic syndrome and glomerulonephritis in severe generalized contact dermatitis caused by poison ivy or poison oak (73).

■ MANAGEMENT

General management strategies are outlined in Table 30.3 (74).

■ SYMPTOMATIC TREATMENT

The inflammation and pruritus of allergic contact dermatitis necessitate symptomatic therapy. For limited, localized allergic contact dermatitis, cool tap water compresses and a topical corticosteroid are the preferred modalities. It is

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safest to use hydrocortisone on the face; however, its use should be limited to a maximum of a few days on the eyelids.

TABLE 30.3 **MANAGEMENT OF ALLERGIC CONTACT DERMATITIS**

Limited, localized reaction	Cool tap water compress
	Topical corticosteroid cream
Extensive, acute reaction	Oral prednisone: 40–60 mg/day initially (adult); allow taper over 10 d–1 mo
Prophylaxis	Antigen avoidance and use of safe alternatives
	Protective clothing
	Barrier cream

When the dermatitis is particularly acute or widespread, systemic corticosteroids can be used. In instances when further exposure can be avoided, such as poison ivy dermatitis, there should be no hesitation in administering systemic corticosteroids. This is a classic example of a self-limited disease that will respond to a course of oral corticosteroid therapy. The popular use of a 6-day decreasing steroid regimen often results in a flare-up of the dermatitis several days after discontinuing the steroids. It is often necessary to continue the treatment for 10 to 14 days or longer. The response to systemic corticosteroids is generally dramatic, with improvement apparent in only a few hours. Three rules that might be applied to systemic corticosteroid therapy in acute contact dermatitis are (a) use an inexpensive preparation such as prednisone; (b) use a high enough initial dosage commensurate with the severity of the rash; and (c) avoid prolonged administration (i.e., more than 1 month).

For secondary infection resulting from scratching because of the pruritus of allergic contact dermatitis, antibiotics may be needed. In addition to oral antibiotics, topical mupirocin can be helpful because this medication rarely causes contact allergy.

PROPHYLAXIS

The physician has a responsibility to his or her patients not only to treat disease but also to prevent it. For that reason, avoid topical applications of medications

that have a high index of sensitization. Included in this group are benzocaine, topical diphenhydramine, neomycin, and bacitracin.

When the offending agent causing allergic contact dermatitis is discovered, a careful instruction must be given to the patient so as to avoid it in the future. The physician should discuss all of the possible sources of exposure and appropriate alternatives free of offending allergen(s). In the case of occupational sensitivity, the list of exposure sources may be quite extensive. When dealing with a plant sensitizer, the patient should be instructed in the proper identification of the offending plant.

Patient education is of paramount importance when treating contact allergy. It has been reported that if the patient is aware of the allergen and informed about the variety of substances that contain it, they are far more likely to improve (75).

There may be instances in which exposure cannot be avoided, either because of the patient's occupation or because of the ubiquitous nature of the allergen. The use of protective clothing is sometimes beneficial; however, barrier creams often will not be useful. Early diagnosis and avoidance of further allergen exposure are critical if chronic, debilitating dermatitis is to be prevented (76).

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Urticaria, Angioedema, and Hereditary Angioedema

CAROL A. SALTOUN

The earliest texts called urticaria and angioedema "a vexing problem" (1). Little has changed since that assessment. Today's clinician is still faced with a common syndrome that affects 20% of the population at some time in their lives (2), but there is no cohesive understanding of the various mechanisms involved or the many clinical presentations or management of the urticarias. For the clinician, this requires a broad knowledge of the many clinical forms of urticaria and an even more extensive familiarity with the creative ways that medications and treatment can be applied. Concepts of allergen-induced cellular inflammation, late-phase cutaneous responses, adhesion molecules, cytokines, inflammatory autocoids, autoantibodies, and as of yet unknown histamine-releasing factors (HRFs) are continuing to lead to a better understanding of pathogenesis and treatment. Meanwhile, clinicians should formulate a rational approach to the care of patients with these conditions.

Urticarial lesions can have diverse appearances. Generally, they consist of raised, erythematous skin lesions that are markedly pruritic, tend to be evanescent in any one location, are usually worsened by scratching, and always blanch with pressure (Fig. 31.1). Individual lesions typically resolve within 24 hours and leave no residual skin changes. This description does not cover all forms of urticaria, but it includes the features necessary for diagnosis in most clinical situations. Angioedema is associated with urticaria in 40% of patients, but the two may occur independently (3). Angioedema is similar to urticaria, except that it occurs in deeper tissues and is often asymmetric. Because there are fewer mast cells and sensory nerve endings in these deeper tissues, pruritus is less common with angioedema, which more typically involves a tingling or burning sensation. Although urticaria may occur on any area of the body, angioedema most often affects the perioral region, periorbital regions, tongue, genitalia, and extremities. In this chapter, angioedema and urticaria are discussed

jointly except where specified.

The incidence of acute urticaria is not known. Although it is said to afflict 10% to 20% of the population at some time during life, it is most common in young adults (1). Chronic urticaria occurs more frequently in middle-aged persons, especially women. If patients have chronic urticaria for more than 6 months, 40% will continue to have recurrent wheals 10 years later (4). The presence of angioedema, severity of symptoms, and evidence of autoimmune mechanism have been shown to prognosticate longer duration of disease; however, race, education, smoking, comorbidity, and atopy did not influence duration (3,5,6). It is likely that the true prevalence of urticaria is higher than reported owing to many acute, self-limited episodes that do not come to medical attention.
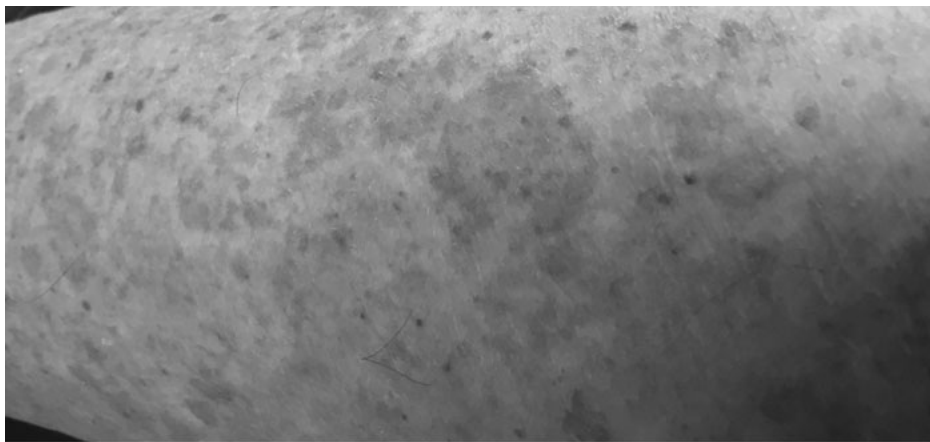
■ **FIGURE 31.1** Typical appearance of urticaria.

Acute urticaria is arbitrarily defined as persisting for less than 6 weeks, whereas chronic urticaria refers to episodes lasting more than 6 weeks. When evaluating chronic urticaria, an etiologic agent or precipitating cause such as a physical urticaria is established in over 30% of patients who are thoroughly evaluated (7–9). However, although considerable progress in determining the pathogenesis of chronic urticaria is being made, most remains idiopathic. In order to distinguish between chronic urticaria that occurs with a known exposure and that without specific triggers, many authors now prefer the term inducible urticaria in place of physical urticaria and the term chronic spontaneous urticaria in place of chronic idiopathic urticaria (10). Success rates of determining an inciting agent are higher in acute forms. Because of the sometimes extreme discomfort and cosmetic problems associated with chronic urticaria, a thorough evaluation to search for etiologic factors is recommended. This evaluation should rely primarily on the history and physical examination as well as response to therapy; limited laboratory evaluation may be indicated based on history and

physical examination findings (Fig. 31.2). In a study of 238 consecutive new patients with chronic urticaria and/or angioedema, subjects were initially worked up with a questionnaire and limited laboratory tests. Subsequently, they were evaluated with a rigorous screening program, including biopsy, extensive blood tests, radiography, provocation tests, and elimination diets. After the rigorous workup, only one patient was found to have a cause for their urticaria that would not have been found with the initial workup alone (11).

PATHOGENESIS

There is no unifying mechanism to account for all forms of urticaria; however, because erythema, edema, and localized pruritus are mimicked by intracutaneous injection of histamine, its release is presumed to be the underlying mediator. The hypothesis that histamine is the central mediator of urticaria is supported by (a) the cutaneous response to injected histamine; (b) the frequent clinical response of various forms of urticaria to therapeutic antihistamines; (c) the documented elevation of plasma histamine or local histamine release from "urticating" tissue in some forms of the condition; and (d) the apparent degranulation of skin mast cells. Tissue resident mast cells or circulating and/or tissue-recruited basophils continue to be the presumed source of the released histamine. Understanding the mechanisms responsible for the release of histamine in the various forms of urticaria remains the focus of current research.

Several potential mechanisms for mast cell activation in the skin are summarized in Table 31.1 and include (a) immunoglobulin E (IgE) immediate hypersensitivity such as occurs with penicillin or foods, (b) activation of the classical or alternative complement cascades such as occurs in immune complex disease like serum sickness or collagen vascular disease, (c) direct mast cell membrane activation such as occurs with injection of morphine or radio contrast media, and (d) generation of thrombin from the extrinsic coagulation pathway with mast cell activation and increase in vascular permeability (12). The presence of major basic protein in biopsy samples of chronic urticaria (13) makes the eosinophil suspect as an effector cell. Prolonged response to histamine, but not leukotrienes, in the skin of patients with chronic urticaria may suggest abnormal clearance of mediators locally (14).

Recent efforts in studying the pathogenesis of chronic urticaria have resulted in the belief that serologic mediators such as autoantibodies or HRFs which are not autoantibodies in addition to/or an alteration in mast cell or basophil responsiveness to histamine-releasing agents can lead to chronic urticaria

(15,16). Evidence for an autoimmune cause of chronic urticaria came to light when it was reported that 14% of patients with chronic idiopathic/spontaneous urticaria had antithyroid antibodies (17). Treatment of these patients with thyroid hormone has not changed the natural course of the disease, but it may have variable benefit to severity and duration of urticarial lesions (18). Because of the association between autoimmune thyroid disease and urticaria, other autoantibodies in patients with chronic urticaria were sought. Greaves reported a 5% to 10% incidence of anti-IgE antibodies in these patients (19). Next, the high-affinity IgE receptor (FcεRI) was identified and isolated. Shortly thereafter, it was reported that 25% to 40% patients with chronic idiopathic/spontaneous urticaria have anti-IgE receptor antibodies that bind to the α subunit of the IgE receptor, causing activation of mast cells or basophils (20). A more recent study of 78 patients with chronic idiopathic/spontaneous urticaria found that one-third of patients had functional (histamine-releasing) autoantibodies directed against either (21). Patients with chronic idiopathic/spontaneous urticaria and the presence of these autoantibodies are classified as chronic autoimmune urticaria (CAU) (22).
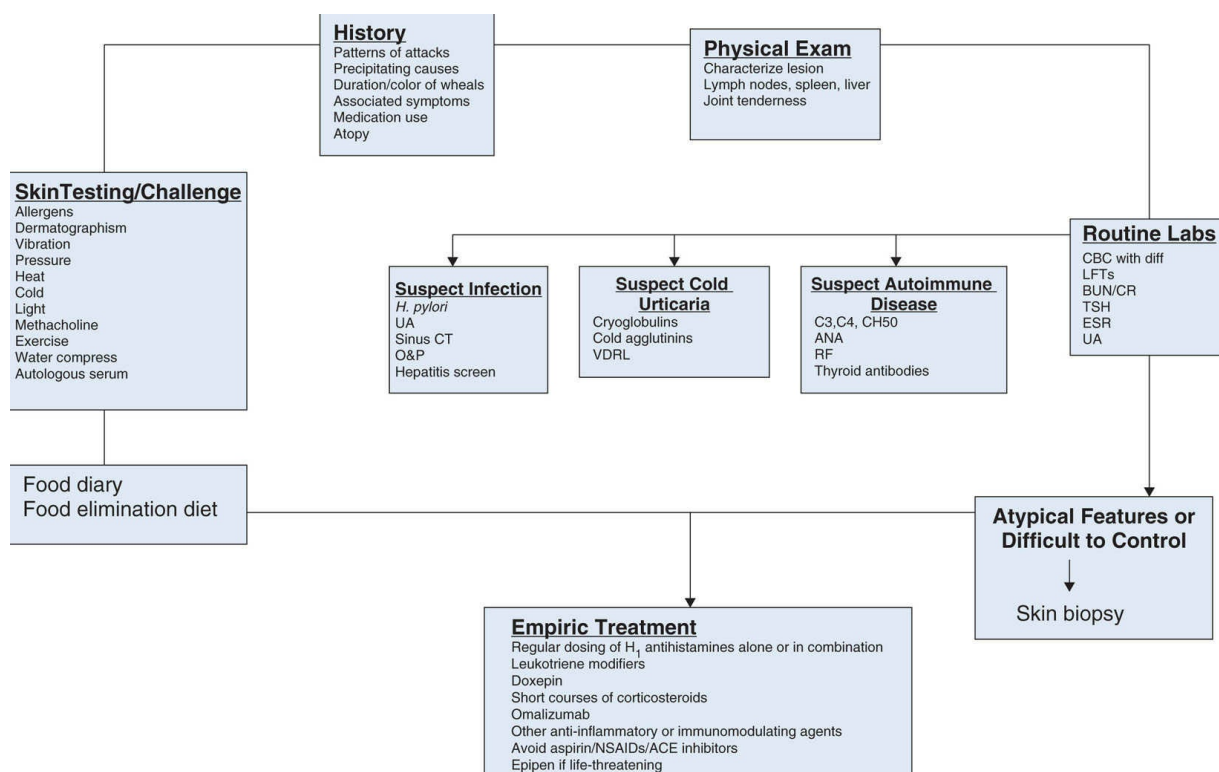
FIGURE 31.2 An algorithm suggesting a potential method for evaluating and treating chronic urticaria. The method includes challenge procedures and laboratory data that may be considered but are not always indicated. Empiric treatment should generally follow the cumulative, sequential use of the medications shown. Avoidance of aspirin, nonsteroidal anti-inflammatory drugs,

and angiotensin-converting enzyme inhibitors is essential. Corticosteroids may be useful for a brief time during the initial treatment until the severity of the urticaria is controlled. ACE, angiotensin-converting enzyme; ANA, anti-nuclear antibody; BUN, blood urea nitrogen; CBC, complete blood count; CR, creatinine; CT, computer tomography; ESR, erythrocyte sedimentation rate; LFTs, liver function tests; NSAID, nonsteroidal anti-inflammatory drugs; O&P, ova and parasites; RF, rheumatoid factor; TSH, thyroid-stimulating hormone; UA, urinalysis; VDRL, Venereal Disease Research Laboratory.

TABLE 31.1 POTENTIAL MECHANISMS OF MAST CELL ACTIVATION IN URTICARIA OR ANGIOEDEMA

TYPE	CAUSE	MEDIATORS
IgE immediate hypersensitivity	Allergens	Histamine, leukotrienes
	Modified IgE	PGD_2, PAF, ECF-A, HRF
	IgG	
	Autoimmune anti-IgE or FcεRlα FcεRII (CD23) on platelets, lymphocytes, or eosinophils	
Activation of classic pathway of complement	Antigen-antibody complexes (IgM IgG_1, IgG_2, or IgG_3)	C3a, C4a, C5a (anaphylatoxins) cause release of mast cell mediators
Activation of alternative pathway of complement	IgA–antigen complexes, complex polysaccharides, lipopolysaccharides	C3a, C4a, C5a (anaphylatoxins) cause release of mast cell mediators
Direct activation of mast cell membrane	Morphine, codeine, polymyxin antibiotics, thiamine, radiocontrast media, certain foods causing histamine release (strawberries, shellfish, ETOH)	Opiates act through specific receptors to release histamine
		Others nonspecifically activate cell membrane to release or generate mast cell mediators

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Plasma-kinin generating system	Activation of plasma and/or tissue kallikrein or coagulation pathway Negatively charged surfaces, collagen vascular basement membrane, or endotoxin	Bradykinin; thrombin activation; especially for HAE and some cases of CIU

CIU, chronic idiopathic urticaria; ECF-A, eosinophil chemotactic factor of anaphylaxis; ETOH, ethanol; HAE, hereditary angioedema; HRF, histamine-releasing factor; IgE, immunoglobulin E; PAF, platelet activating factor; PGD_2, prostaglandin D_2.

The presence and clinical relevance of autoantibodies to FcεRI or IgE can be identified by both *in vivo* and *in vitro* tests. The autologous serum skin test (ASST) consists of a cutaneous injection of autologous serum resulting in a wheal-and-flare at 30 minutes; however, healthy patients without urticaria have been found to have positive ASST (23). Owing to the occurrence of immunoreactive but nonhistamine-releasing autoantibodies in some chronic idiopathic/spontaneous urticaria patients and their presence in patients with autoimmune connective tissue diseases without chronic idiopathic/spontaneous urticaria, immunoassays for these antibodies have not been useful. Instead, methods for measuring the release of histamine have been developed where the sera of patients with chronic idiopathic/spontaneous urticaria is incubated with donor basophils, then measured directly for histamine or indirectly through basophil activation marker CD203c (24). These assays are limited by the variability of releasability between donor basophils from different sources.

The suggestion of the presence of a nonantibody HRF, such as complement, chemokines, or cytokines, comes from the finding that over 50% of chronic idiopathic/spontaneous urticaria patients do not have autoantibodies. In support of this notion, it has been shown that IgG-depleted serum can cause a positive ASST (25). Evidence for alterations in basophil function comes from the finding of two basophil phenotypes in patients with chronic idiopathic/spontaneous urticaria with differing IgE receptor responsiveness (26). In addition to differences in histamine releasability, patients with chronic idiopathic/spontaneous urticaria have been found to have decreased numbers of serum basophils which suggests that basophils are recruited to the skin in chronic idiopathic/spontaneous urticaria (27,28). This was confirmed by observations that both lesional and nonlesional skin of patients with CAU contained increased basophils after ASST compared to healthy controls (29).

Excessive production of bradykinin, a potent vasodilator, is the cause of

swelling in hereditary angioedema (HAE) (30,31) and angioedema resulting from angiotensin-converting enzyme (ACE) inhibitors (32). In addition, bradykinin has been reported to be capable of causing a wheal-and-flare reaction when injected into human skin. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are capable of altering arachidonic acid metabolism and can result in urticaria without specific interaction between IgE and the pharmacologic agent.

Nonspecific factors that may aggravate urticaria include fever, heat, alcohol ingestion, exercise, emotional stress, perimenopausal status, and hyperthyroidism. Anaphylaxis and urticaria caused by progesterone have been described (33,34), but seem to be exceedingly rare, and progesterone has been used to treat chronic cyclic urticaria and eosinophilia (35). Certain food additives, such as tartrazine or monosodium glutamate, have been reported to aggravate chronic urticaria (36). Many experts experienced in urticaria believe that progesterone is not a cause or a treatment and that food preservatives do not aggravate chronic urticaria. There have been studies showing no relationship between urticaria and monosodium glutamate as well as aspartame (37,38).

BIOPSY

Biopsy of urticarial lesions has accomplished less than expected to improve our understanding of the pathogenesis of urticaria, but may help guide therapy in refractory cases. Three major patterns are currently recognized (Table 31.2). Acute and physical/inducible urticarias show only dermal edema without cellular infiltrate, whereas chronic urticaria typically shows a perivascular mononuclear or lymphocytic infiltrate with an increased number of mast cells. Urticarial vasculitis—in which lesions last more than 24 hours, may be purpuric, and may heal with residual hyperpigmentation—shows neutrophil infiltration and vessel wall necrosis with or without immunoprotein deposition. A subset of patients (up to 19% in one study) with acute or chronic urticaria will have a neutrophil predominant dermal infiltrate without evidence of vasculitis (39).

Studies of the cellular infiltrate of chronic idiopathic/spontaneous urticaria patients both with and without functional antibodies to FcεRIα found no difference in either the type or number of inflammatory cells or the cytokine pattern between the two groups. In addition, the histologic findings were similar to that of the late-phase reaction in atopic individuals. Chronic idiopathic/spontaneous urticaria skin biopsies demonstrated increased levels of interleukin (IL)-4, IL-5, and interferon-γ (INF-γ), whereas late-phase reaction

biopsies revealed increased IL-4, IL-5, but not IFN-γ, suggesting the involvement of a mixture of T_H1 and T_H2 cells or, alternatively, T_H0 cells in chronic idiopathic/spontaneous urticaria (40).

CLASSIFICATION

Classification in terms of known causes is helpful in evaluating patients with urticaria. Table 31.3 presents one classification that may be clinically useful. A recent European Position Paper and an updated American Practice Parameter on acute and chronic urticaria provide additional structured recommendations for classification (41,42).

Nonimmunologic

Physical/Inducible Urticaria

The physical urticarias, more recently referred to as the inducible urticarias to emphasize that they are induced by environmental stimuli, are present in 20% to 30% of adults with chronic urticaria, and several reviews have been published (9,43–46). Physical/inducible urticarias are considered a subset of chronic urticaria and can be present as the only cause of chronic urticaria or more than one type may occur together in the same patient. Most forms, with the exception of delayed pressure urticaria (DPU), occur as simple hives without inflammation, and individual lesions resolve within 24 hours. As a group, they can be reproduced by various physical stimuli that have been standardized in some cases (Table 31.4).

TABLE 31.2 BIOPSY PATTERNS OF URTICARIAL AND ANGIOEDEMA LESIONS

TYPE	DESCRIPTION
Acute urticaria/angioedema	Dilation of small venules and capillaries in superficial dermis (urticaria) or subcutaneous tissue (angioedema); flattening of rete pegs; swollen collagen fibrils
Chronic idiopathic/spontaneous urticaria	Mild cellular inflammation, including activated T-lymphocytes, monocytes, and mast cells; delayed-onset urticaria may be mediated by cytokines, e.g., IL-1, IL-3, IL-5, or HRF
Urticarial vasculitis	Neutrophil infiltration with vessel wall necrosis;

occasional deposition of immunoglobulin and complement

HRF, histamine-releasing factor; IL-1, interleukin 1.

TABLE 31.3 CLASSIFICATION OF URTICARIA

NONIMMUNOLOGIC

PHYSICAL URTICARIAS	HEREDITARY URTICARIA	MISCELLANEOUS
Dermatographism	Hereditary angioedema	Infections
Adrenergic	Hereditary vibratory angioedema	Vasculitis
Pressure		Neoplasm
Vibratory	Urticaria, deafness, amyloidosis syndrome	Anaphylaxis
Solar	Familial localized heat urticaria	Recurrent idiopathic/spontaneous
Cholinergic		Exercise induced
Local heat	C3b inactivator deficiency	
Cold	Porphyria	
	Papular urticaria	
	Urticaria pigmentosa	

IMMUNOLOGIC

Food	Transfusion reactions
Drugs	Schnitzler syndrome
Autoimmune anti-IgE and/or anti-FcεRI	Atopy
	Acquired C1 INH deficiency
Insect stings	

IDENTIFIABLE AGENTS (UNCERTAIN MECHANISMS)

Aspirin	Radiocontrast media
Opiates	

Dermatographism literally means "write on skin." This phenomenon, also called factitious urticaria, may be detected unexpectedly on routine examination, or patients may complain of pruritus and rash, frequently characterized by linear wheals. When questioned carefully, they may state that itching precedes the rash, causing them to scratch and worsen the condition. The cause of this lesion is unknown. Because it occurs in approximately 5% of people, the majority of whom do not have associated pruritus, it may be a normal variant. Its onset has been described following severe drug reactions. A delayed form has been recognized with onset of lesions 3 to 8 hours after stimulus to the skin, which may be related to DPU. It may accompany other forms of urticaria. The lesion is readily demonstrated by lightly stroking the skin of an affected patient with a pointed instrument or tongue depressor. This produces erythema, pruritus, and linear streaks of edema or wheal formation. No antigen, however, has been shown to initiate the response, but dermatographism has been passively transferred with plasma (47). Antihistamines usually ameliorate symptoms if they are present. Cutaneous mastocytosis may be considered under the heading of dermatographism, because stroking the skin results in significant wheal formation (Darier sign). This disease is characterized by a diffuse increase in cutaneous mast cells. The skin may appear normal, but is usually marked by thickening and accentuated skin folds.

TABLE 31.4 TEST PROCEDURES FOR PHYSICAL AND CHRONIC IDIOPATHIC/SPONTANEOUS URTICARIA

URTICARIA TYPE	PROCEDURE
Dermatographism	Firmly stroke interscapular skin with tongue blade or dermatographometer.
Delayed pressure urticaria	Hang 15-pound weight across shoulder while walking for 20 min.
Solar urticaria	Expose skin to defined wavelengths of light.
Cholinergic urticaria	1. Methacholine skin test 2. Immersion in hot bath (42°C) to raise body temperature

	0.7°C
Local heat urticaria	Apply warm compress to forearm.
Cold urticaria	3. Apply ice cube to forearm for 4 min; observe rewarming for 10 min.
	4. Exercise in cold and observe for cholinergic-like urticaria (cold-induced cholinergic urticaria).
Aquagenic	Apply water compress (35°C) for 30 min.
Vibratory	Laboratory vortex applied gently to mid-forearm for 4 min.
Autoimmune	Intradermal injection of autologous serum.

DPU, with or without angioedema, is clinically characterized by the gradual onset of wheals or edema in areas where pressure has been applied to the skin, such as from the strap of a heavy bag or a tight belt. Onset is usually 4 to 6 hours after exposure, but wide variations may be noted. An immediate form of pressure urticaria has been observed. The lesion of DPU can be reproduced by applying pressure with motion for 20 minutes (48). DPU lesions can be pruritic and/or painful and may be associated with malaise, fever, chills, arthralgias, and leukocytosis. The mechanism of these reactions is unknown, but biopsy samples of lesions show a predominantly eosinophilic cell infiltrate located in the deep dermis (49). In addition, increased levels of tumor necrosis factor-α (TNF-α) have been found in many cell types of patients with DPU (50). A case report demonstrated successful treatment of DPU with anti-TNF-α, suggesting that TNF-α may play an important role in DPU (51). The incidence of DPU has been reported as 2% of all urticarias; however, one study has found that 37% of patients with chronic idiopathic/spontaneous urticaria have associated DPU (6,52). Treatment is based on avoidance of situations that precipitate the lesions. Antihistamines are generally ineffective, and a low-dose, alternate-day corticosteroid may be necessary for the more severe cases. Dapsone (52), montelukast (53), sulfasalazine (54), selective serotonin reuptake inhibitors (55) and omalizumab (56) have been beneficial in case reports and case series.

Solar urticaria is clinically characterized by development of pruritus,

erythema, and edema within minutes of exposure to light. The lesions are typically present only in exposed areas, but can occur in areas covered by thin clothing. Diagnosis can be established by using broad-spectrum light with various filters or a spectrodermograph to document the eliciting wavelength (57). Solar urticaria can be confused with and should be distinguished from the more commonly occurring polymorphous light eruption as well as cutaneous lupus erythematous that can develop after sun exposure. Treatment includes avoidance of sunlight and use of protective clothing and various sunscreens or blockers, depending on the wavelength eliciting the lesion. An antihistamine taken 1 hour before exposure may be helpful in some forms, and induction of tolerance is possible (58). Omalizumab has been successful in controlling solar urticaria in several reports (59).

Cholinergic urticaria (also called generalized heat urticaria) is a common form of urticaria, occurring in 5% to 7% of patients with chronic urticaria and is even more common in teenagers and young adults (11.2%). It is clinically characterized by small, punctate hives surrounded by an erythematous flare, the so-called "fried egg" appearance. These lesions may be clustered initially, but can coalesce and usually become generalized in distribution, primarily over the upper trunk and arms. Pruritus is generally severe. The onset of the rash is frequently associated with hot showers, sudden temperature change, exercise, sweating, or emotional stress. Rarely, systemic symptoms may occur (60). The mechanism of this reaction is not certain, but cholinergically mediated thermodysregulation resulting in a neurogenic reflex has been postulated because it can be reproduced by increasing the core body temperature. In addition to histamine and other mast cell mediators, increased muscarinic receptors have been reported in lesional sites of a patient with cholinergic urticaria (61). The appearance and description of the rash are highly characteristic and can be reproduced by an intradermal methacholine skin test, but only in one-third of the patients (62). Exercise wearing warm clothing or submersion in a warm bath is a more sensitive method of reproducing the urticaria. Passive heat can be used to differentiate this syndrome from exercise-induced urticaria or anaphylaxis. Nonsedating antihistamines are the treatment of choice; however, some patients require combination treatment, including a first-generation antihistamine, such as hydroxyzine. Omalizumab has been reported to successfully control cholinergic urticaria (63).

A form of "autonomic" urticaria called *adrenergic urticaria* has been described and can be reproduced by intracutaneous injection of noradrenaline (3 to 10 ng in 0.02 mL saline) (64). This unique form of urticaria is characterized

by a "halo" of white skin surrounding a small papule. It may have been previously misdiagnosed as cholinergic urticaria because of its small lesions and its association with stress. In this case, however, relief can be provided with β-blockers.

Local heat urticaria, a rare form of heat urticaria (65), may be demonstrated by applying localized heat to the skin for 5 minutes. A familial localized heat urticaria has also been reported (66) and is manifested by a delay in onset of urticarial lesions of 4 to 6 hours following local heat exposure.

Cold urticaria is clinically characterized by the rapid onset of urticaria or angioedema after cold exposure (46). It more frequently affects young adults, and higher incidences are reported in colder climates. Although it is usually a self-limited disorder lasting on average 6 years (67), some patients will have persistent symptoms. Lesions are generally localized to exposed areas, but sudden total body exposure, as in swimming, may cause hypotension and result in death (68). Although usually idiopathic (primary acquired cold urticaria), cold urticaria has been associated with cryoglobulinemia, cryofibrinogenemia, cold agglutinin disease, and paroxysmal cold hemoglobinuria (secondary acquired cold urticaria) (69). The mechanism of cold urticaria is not known. Release of histamine and several other mediators as well as lack of a late-phase cellular infiltrate has been demonstrated in selected patients on biopsy (70). A case report describes the successful treatment of cold-induced urticaria with omalizumab, suggesting a possible role for IgE and FcεRI in its pathogenesis (71). In patients with abnormal proteins, passive transfer of the cold sensitivity has been accomplished using plasma (72). Some cryoprecipitates can fix complement, and thus may induce anaphylatoxin production (73). Diagnosis of cold urticaria can often be confirmed by placing an ice cube on the forearm for 4 minutes (Table 31.4); however, this diagnostic test can be negative in some forms. If cryoglobulins are present, a search should be performed for an underlying cause, for example, hepatitis B or C infection or lymphoreticular malignancy. Avoidance strategies should consist of limited cold exposure, cautious exposure to cold water when swimming, proper clothing, including covering the face and extremities when exposed to cold, caution against holding and consuming cold foods and beverages and warning health care providers of the condition because intravenous administration of cold solutions can induce symptoms. Historically, treatment has included oral cyproheptadine (74); however, other H_1 antihistamines, including cetirizine and desloratidine, are also effective and have less side effects (75). Patients at risk for systemic symptoms should carry an epinephrine autoinjector. In cases in which an abnormal protein

is present, treatment of the underlying disease may be indicated and curative.

Aquagenic urticaria is rare form of physical/inducible urticaria that tends to have a higher incidence in women, and age of onset is typically shortly after puberty. Hives appear soon after direct contact with water regardless of type (tap, distilled, sweat, and saline) or temperature of water. The pathogenesis of aquagenic urticaria is unclear. Diagnosis can be made by applying a compress of water that is at room temperature to avoid confusion with cold- or heat-induced urticaria. The initial treatment of choice for aquagenic urticaria is an H_1 antihistamine (76); however, if symptoms are not controlled, treatment with propranolol, 10 to 40 mg daily, has been reported to be effective (77).

Inherited Angioedema

HAE is clinically characterized by recurrent spontaneous or trauma-induced episodes of angioedema involving any part of the body lasting 2 to 5 days. Pruritus or urticaria is not features of this disease. Laryngeal edema is common and is the major cause of death. Angioedema of the gastrointestinal tract may cause abdominal discomfort and can mimic an acute abdomen. The cause of angioedema in HAE is due to excessive production of bradykinin, which is a potent vasodilator. HAE type I is inherited as an autosomal dominant trait, manifested by a decrease in expression of C1-inhibitor (C1-INH) in the plasma. HAE type II is characterized by expression of a dysfunctional C1-INH with normal plasma levels. Two additional subtypes of HAE have been defined that are distinguished by having normal C1-INH plasma levels and activity. Those with specific mutations in the factor XII gene have been classified as HAE with normal C1-INH and a factor XII mutation (FXII-HAE) and those with unknown cause as HAE with normal C1-INH of unknown cause (U-HAE) (78,79). C1-INH plays a role in limiting the production of bradykinin via the contact system by inactivation of plasma kallikrein and factor XII. Deficient or dysfunctional C1-INH can result in unchecked bradykinin production. This knowledge paired with the finding of increased bradykinin levels in the plasma of patients with HAE during attacks suggests that the primary mediator of HAE is bradykinin produced through the contact system (80). The specific trigger that initiates local activation of the contact system that leads to angioedema remains unclear. While low levels of C4 are found in patients with deficient or dysfunctional C1-INH, it does not have a role in the pathogenesis of HAE.

The diagnosis of HAE is usually established by a history of angioedema, a family history of similar disease or early death because of laryngeal obstruction, and appropriate complement studies (Table 31.5). The usual forms of treatment

for angioedema, including epinephrine, corticosteroids, and antihistamines, are generally ineffective for HAE. Tracheostomy may be necessary in urgent situations where laryngeal edema has occurred. Supportive therapy, such as intravenous fluids or analgesics, may be required for other manifestations of the disease.

Treatment of patients with HAE is aimed at avoiding mortality and reducing morbidity. Early treatment at onset of swelling has been shown to improve efficacy (81). First-line therapy for severe, acute attacks of HAE includes replacement therapy with plasma derived (20 units/kg) or recombinant (50 units/kg) C1-INH concentrate. Dose is based on patient weight and is administered intravenously with an average time to onset of relief of 2 hours (82). C1-INH concentrate is also safe for use in children, pregnant women, and for prophylaxis in surgery (83). Icatibant, a bradykinin B_2-receptor antagonist, acts by selectively and competitively antagonizing the bradykinin B_2 receptor. It can be self-administered at a dose of 30 mg subcutaneously with median time to $\geq 50\%$ reduction of 2 hours (84). Ecallantide, a genetically engineered recombinant plasma kallikrein inhibitor, blocks production of bradykinin by inhibiting plasma kallikrein. The adult dose consists of three 10 mg injections given at separate sites. Ecallantide should be administered by a clinician equipped to manage anaphylaxis because allergic reactions were reported in 2% to 3% of patients (85). In the absence of one of the above first-line agents, fresh frozen plasma, which contains C1-INH, can also be used in acute attacks, but rarely can cause worsening of symptoms because it also contains high-molecular-weight kininogen, which can increase bradykinin production. Esterase-inhibiting drugs such as epsilon amino caproic acid (5 g every 6 hours) and tranexamic acid (not available in the United States, but given orally) have been used to treat acute attacks in efforts to slow complement activation; however, these agents require up to 48 hours to have an effect (86,87).

TABLE 31.5 DIAGNOSIS OF THE DIFFERENT FORMS OF HEREDITARY AND ACQUIRED ANGIOEDEMA

	MECHANISM	DIAGNOSIS
HAE with C1-INH deficiency (C1-INH HAE type I) (85% of HAE)	Autosomal codominant deficiency of C1-INH bradykinin-mediated angioedema	Low C4 when asymptomatic Low or absent C2 during an attack Low or absent C1-INH level and function

HAE with C1-INH deficiency (C1-INH HAE type II) (15% of HAE)	Functionally inactive C1-INH	Normal level of C1-INH, but low functional activity (functional assay required) Low C4 Low or absent C2 during attacks
HAE with factor XII deficiency (FXII-HAE)	Factor XII gene mutation	Normal C4 Normal C1-INH level and function
HAE of unknown origin (U-HAE)	Unknown	Normal C4 Normal C1-INH level and function
Acquired angioedema	Reduced C1q levels by excessive activation of C1 (e.g., lymphoma) through C1 INH absorption and/or consumption	Low C1q levels Low C1-INH level Low C4 Absent family history
Autoimmune-acquired angioedema	Autoantibody (IgG) against C1-INH	Low C1q Low C1-INH level Low C4 Absent family history

HAE, hereditary angioedema; IgG, immunoglobulin G; INH, inhibitor.

For patients who suffer from frequent episodes of HAE, long-term prophylaxis should be considered. Regular infusions (every 3 to 4 days) of plasma derived or recombinant C1-INH are effective in reducing frequency of attacks but can be expensive. Attenuated androgens such as Danazol (88) have been used successfully on a chronic basis to treat HAE. Attenuated androgens appear to upregulate the synthetic capability of hepatic cells that make C1-INH with a corresponding increase in C4 level and reduction of the number and severity of acute attacks. Often, sufficient clinical improvement may be obtained

with minimal doses such that the C4 level is normalized, but the C1-INH level is not significantly increased. Initial treatment with 200 mg two to three times a day of Danazol should be used to control symptoms and then decreased as tolerated. Long-term low (minimal) dose of danazol at 200 mg/day is safe; however, side effects of attenuated androgens include abnormal liver function, lipid abnormalities, weight gain, amenorrhea, acne, hirsutism, and, rarely, peliosis hepatitis. One woman given attenuated androgens during the last 8 weeks of pregnancy experienced no ill effects, and virilization of the infant was transient (89). Monitoring of liver functions, a complete blood count (CBC) and urinalysis should occur every 6 months for patients taking long-term androgen therapy (90). For acute attacks, danazol 600 to 800 mg at onset of swelling can also be used if no other agent is available.

The acquired forms of C1 inhibitor deficiency (C1INH-AAE) result from increased destruction or metabolism of C1 inhibitor. Destruction occurs when autoantibodies directed against the C1 inhibitor are produced, bind to its active site, and cause inactivation. Alternatively, anti-idiotypic antibodies are produced against specific B-cell surface immunoglobulins, leading to immune complex formation and continuous C1 activation (91). Large quantities of C1 inhibitor are subsequently consumed, causing a deficit and thus the symptoms of C1 inhibitor deficiency. This acquired type of deficiency occurs in older patients compared to the younger onset of HAE and is usually associated with autoimmune disorders, such as systemic lupus erythematous, autoimmune hemolytic anemia and cryoglobulinemia, malignancy, or B-cell lymphoproliferative disorders, such as multiple myeloma, leukemia, and monoclonal gammopathy of undetermined significance (MGUS) (92). Fewer than 10% of cases of acquired angioedema are not associated with an underlying disorder (93). As in the hereditary forms of the disease, C1, C2, and C4 inhibitors are low, but only in the acquired forms is C1q also depressed. Acute attacks in these patients can be treated similarly to HAE; however, therapy should be directed at the underlying lymphoproliferative or autoimmune disorder because this often reduces frequency of attacks and can reverse C1-INH deficiency.

Hereditary vibratory angioedema is clinically characterized by localized pruritus and swelling in areas exposed to vibratory stimuli (94). It appears to have an autosomal dominant inheritance, and for one form of vibratory urticaria, a gain-of-function mutation in the ADGRE2 gene has been identified (95). Treatment consists of avoidance of vibratory stimuli and use of antihistamines in an attempt to reduce symptoms.

Other Forms of Urticaria and Angioedema

Papular urticaria is clinically characterized by slightly erythematous, highly pruritic linear papular lesions of various sizes. Lesions tend to start off as urticarial, but become persistent and papular; a central punctum is often present. The lower extremities are involved most often, although the trunk may also be affected, especially in young children. The immunologic mechanism is unknown, but the rash is thought to be caused by hypersensitivity to the saliva, mouth parts, or excreta of biting insects, such as mosquitoes, bedbugs, fleas, lice, and mites. Treatment is supportive: antihistamines are given, often prophylactically, in an attempt to reduce pruritus. Good skin care is essential to prevent infection caused by scratching. Examination of a person's sleeping quarters and children's play areas for insects may provide a clue to the etiology. Pruritic urticarial papules and plaques of pregnancy are an extremely pruritic condition of primigravida women that occurs in the third trimester. Lesions begin in the striae distensae and spread up and around the umbilicus, thighs, and buttocks. In some atypical cases, biopsy should be performed to distinguish the diagnosis from herpes gestationis.

Urticaria Pigmentosa

Urticaria pigmentosa is characterized by persistent, red-brown, maculopapular lesions that urticate when stroked (Darier sign). These lesions generally have their onset in childhood. Rare familial forms have been described. Biopsy shows mast cell infiltration (96). The diagnosis may be established by their typical appearance, Darier sign, and skin biopsy. Occasionally, urticaria pigmentosa can complicate other forms of anaphylaxis, such as *Hymenoptera* venom sensitivity, causing very severe reactions with sudden vascular collapse. These cutaneous lesions may occur in patients with systemic mastocytosis, a generalized form of mast cell infiltration into bone, liver, lymph nodes, and spleen.

The remaining forms of urticaria are associated with many diverse etiologies (Table 31.3). Diagnosis is established by history and physical examination based on knowledge of the possible causes. Laboratory evaluation is occasionally helpful in establishing a diagnosis and identifying the underlying disease. Treatment is based on the underlying problem, and may include avoidance, antihistamines, and corticosteroid therapy or other forms of anti-inflammatory drugs.

Clinical Approach

The clinical history is the single most important aspect of evaluating patients with urticaria. The history generally provides important clues to the etiology; therefore, an organized approach is essential.

If the patient has no rash at the time of evaluation, urticaria or angioedema can usually be established historically with a history of hives or welts, resembling mosquito-bite–like lesions; raised, erythematous, pruritic lesions; evanescent symptoms; potentiation of lesions by scratching; and lesions that may coalesce. By contrast, angioedema is asymmetric, often involves nondependent areas, recurs in different sites, is transient, and is associated with little pruritus. Urticaria and angioedema may occur together. Cholinergic or adrenergic urticaria, papular urticaria, dermatographism, urticaria pigmentosa, and familial cold urticaria, however, do not fit the typical pattern.

Both papular urticaria and urticaria pigmentosa most often arise in childhood. HAE and hereditary vibratory angioedema may also occur during childhood, but are readily recognized by the absence of urticaria in both diseases. Other etiologic factors in childhood urticaria have been reviewed (45,97,98).

Once the diagnosis of urticaria is established on the basis of history, etiologic mechanisms should be considered. The patient with dermatographism usually reports a history of rash after scratching. Frequently, the patient notices itching first, scratches the offending site, and then develops linear wheals. Stroking the skin with a pointed instrument without disrupting the integument confirms the diagnosis. With most patients, the physical/inducible urticarias may be eliminated quickly as a possible diagnosis merely by asking about the temporal association with light, heat, cold, pressure, or vibration, or by using established clinical tests (Table 31.4). Cholinergic urticaria is usually recognized by its characteristic lesions and relationship to rising body temperature or stress. Hereditary forms of urticaria are rare. Familial localized heat urticaria is recognized by its relationship to the local application of heat, and familial cold urticaria by the unusual papular skin lesions and the predominance of a burning sensation instead of pruritus. Thus, after a few moments of discussion with a patient, a physical/inducible urticaria or hereditary form can usually be suspected or established.

The success of determining an etiology for urticaria is most likely a function of whether it is acute or chronic because a cause is discovered much more frequently when it is acute. Each of the causes presented in Table 31.3 may be involved. Food may be identified in acute urticaria. Great patience and effort are

necessary, along with repeated queries to detect drug use. Over-the-counter preparations are not regarded as drugs by many patients, and must be specified when questioning the patient. Whereas penicillins are a common cause of urticaria, aspirin and other nonselective NSAIDs can trigger acute urticaria within minutes to 3 hours after ingestion or can cause exacerbations of chronic idiopathic/spontaneous urticaria in some patients. Drug-induced episodes of urticaria are usually of the acute type. ACE inhibitors are a common cause of angioedema without urticaria or pruritus, affecting up to 0.7% of recipients in some studies (99). Patients with ACE inhibitor–induced angioedema have been found to have elevated bradykinin levels (32). Reactions to ACE inhibitors usually occur within 1 week of initiating therapy, but can occur at any time, including after years of treatment. Angiotensin II receptor blockers are believed to have no effect on bradykinin production. Although theoretically they should not cause angioedema and are considered a safe alternative, several case reports have been published (100,101). Although rare, infections documented as causes of urticaria include infectious mononucleosis, viral hepatitis (both B and C), and fungal and parasitic invasions (102,103). If the history does not reveal significant clues, the patient's urticaria generally is labeled chronic idiopathic/spontaneous urticaria. Most patients with chronic urticaria fall into this category.

Physical Examination

A complete physical examination should be performed on all patients with urticaria. The purpose of the examination is to identify typical urticarial lesions, if present; to establish the presence or absence of dermatographism; to identify the characteristic lesions of cholinergic and papular urticaria; to characterize atypical lesions; to determine the presence of jaundice, urticaria pigmentosa (Darier sign), or familial cold urticaria; to exclude other cutaneous diseases; to exclude evidence of systemic disease; and to establish the presence of coexisting diseases.

Diagnostic Studies

It is difficult to outline an acceptable diagnostic program for all patients with urticaria. Each diagnostic workup must be individualized, depending on the results of the history and physical examination. An algorithm may be useful in this often unrewarding diagnostic endeavor (Fig. 31.2).

Foods

Various diagnostic procedures may be considered when food is thought to be a cause of urticaria (Table 31.6). These include (a) avoidance, (b) restricted diet,

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(c) diet diary, (d) skin testing with food extracts or fresh foods, and (e) food challenge.

Skin Tests

Routine food skin tests used in evaluating urticaria are rarely useful. Because the etiology of chronic urticaria is established in only the minority of patients, very few of these cases will be related to food such that the diagnostic yield from skin testing is very low. In unselected patients, the positive predictive value of skin tests is low. Important studies of food-induced atopic dermatitis have revealed a few selected foods that are most commonly associated with symptoms (104). These include eggs, peanuts, fish, soy, pork, milk, wheat, beef, and chicken. If no food skin test results are positive, then foods are probably not a cause. If all food skin test results are positive, dermatographism is probably present. Some foods can cause fluctuations in symptoms of chronic urticaria because of histamine content or ability to cause release of histamine. These foods have been termed pseudoallergens, and their relevance is supported by the observation that once urticaria is in remission, patients are able to tolerate these foods without recurrence (105). At present, an extensive battery of food tests is not recommended on a routine basis, and must be used with clinical discretion. Commercially prepared extracts frequently lack labile proteins responsible for IgE-mediated sensitivity to many fruits and vegetables. If the clinical history is convincing for a food allergy, but skin testing with a commercially prepared extract is negative, testing should be repeated with the fresh food before concluding that food allergen–specific IgE is absent (106). Evaluation of the serum for specific IgE by immunoassay may be used in place of skin testing. Although it is considered less sensitive, it may be necessary when a patient has an exquisite sensitivity to a certain food or significant dermatographism or when antihistamines cannot be discontinued.

TABLE 31.6 DIAGNOSTIC STUDIES OF FOOD-INDUCED URTICARIA

STRATEGY	PROCEDURE	OUTCOME
Avoidance (acute)	Use patient history to eliminate 1 or 2 foods	Urticaria should clear with avoidance
Restricted diet (chronic relapsing)	Use standardized rice/lamb or other restrictive diets; elemental diet may be useful	Reinstitute one food every 3–5 d; repeat if successful until allergen is identified

Diet diary for intermittent episodes	List all foods and events for 24 h prior to episode on several occasions	Eliminate suspected food, hives should not recur
Skin tests to suspected true allergens	Use a brief battery of food skin tests based on patient's history; certain inhalant or latex allergens may suggest cross-reacting foods	Eliminate suspected test positive foods; a battery of negative skin tests suggests no food hypersensitivity
Double-blind, placebo-controlled food challenge	Gold standard; especially useful when the patients' perceptions may bias accurate symptom assessment	

Drugs

With the exception of penicillins, foreign sera, and recombinant proteins such as insulin, there are no reliable diagnostic tests for predicting or establishing clinical sensitivity to a drug. In patients with urticaria, drugs must always be considered as etiologic agents. The only evaluation of value is avoidance of the drug. This can be accomplished safely and effectively in most patients, even when multiple drugs are involved and coexisting diseases are present. Substitute drugs with different chemical structures are frequently available and may be used. Not all drugs need to be stopped simultaneously unless the allergic reaction is severe.

Infections

As noted previously, viral infections such as hepatitis B and C, bacterial infections, fungal infections, and parasites have all been reported to cause urticaria. Patients with infectious mononucleosis or hepatitis or *Helicobacter pylori* colonization generally have other symptoms, and appropriate laboratory studies confirm the diagnosis. The demonstration of anti-*H. pylori* IgG or IgM antibodies has been found in as many as 70% of patients with chronic idiopathic/spontaneous urticaria, but treatment has had variable effect on urticarial lesions (103,107). This finding questions a shared pathogenic mechanism, such as molecular mimicry. Routine physical examination should

include a search for tinea pedis, capitas, or thrush to rule out fungal infection as the possible cause. Many of the parasitic infections will be associated with peripheral blood eosinophilia, high serum IgE concentrations, or positive stool specimens. An extensive search for occult infection is of no value. If history or examination suggests undiagnosed infection, appropriate laboratory studies should be undertaken (Fig. 31.2).

Penetrants

The medical literature is filled with numerous case reports of urticaria following contact. The only tests to be performed involve actual contact with the agent and demonstration of a localized skin eruption in the area of contact. Usually, these cases of urticaria result from penetration of the skin by antigen or a mediator-releasing substance from animal hairs or stingers. Examples of agents causing such urticaria include latex, foods, drugs, and occupationally used chemicals (108).

Insect Stings

Urticaria may present as a result of insect stings, and this history generally is obtained easily. Appropriate skin tests with Hymenoptera venoms may be indicated in cases of generalized urticaria and anaphylaxis to demonstrate immediate hypersensitivity. One should consider fire ant stings owing to their continued migration into more northern latitudes. Whole-body extract skin testing or an immunoassay for IgE to venom may be helpful diagnostically.

Neoplasm

One population-based cohort study from Taiwan reported an increased cancer risk (standardized incidence ratio of 2.2) in patients with chronic urticaria. The risk was highest in those aged 20 to 39. If neoplasm is suspected by history or examination, standard evaluation should be undertaken (109).

Vasculitis

In a patient who has urticarial lesions that last for more than 24 hours, result in burning rather than pruritus, leave residual scarring, or appear petechial in nature, vasculitis should be suspected. A CBC, sedimentation rate, urinalysis, and tissue biopsy are indicated. Tests for antinuclear antibody and rheumatoid factor, complement studies, and screening for hepatitis and mononucleosis are generally indicated. Urticarial vasculitis must be differentiated from chronic idiopathic/spontaneous urticaria, and if diagnosed, evaluation for associated systemic disease should be performed (110).

Acute urticaria in association with arthralgias, fever, and lymphadenopathy developing 1 to 3 weeks following drug exposure, insect sting, or heterologous serum administration is suspicious for serum sickness. CBC, urinalysis, and a sedimentation rate are indicated. Serum concentrations of C3, C4, and total hemolytic complement are depressed, indicating that immune complexes are involved in the pathogenesis of this disease.

Idiopathic/Spontaneous Chronic Urticaria

The more difficult and more common problem regarding diagnostic tests relates to those patients who appear to have idiopathic disease. Laboratory studies are probably unnecessary in the absence of abnormal features in the history or physical examination (111). Most of these episodes are self-limited and resolve spontaneously.

In some patients with chronic idiopathic/spontaneous urticaria, the discomfort, inconvenience, and disfigurement of the disease generally warrant further evaluation. The following tests should be considered but not necessarily performed in all patients: CBC with differential, urinalysis, sedimentation rate, complement studies, examination of stool for ova and parasites, antinuclear antibody, Venereal Disease Research Laboratory testing, hepatitis screen, and skin biopsy. Because thyroid disease (particularly Hashimoto thyroiditis) is more common in chronic urticaria, thyroid function testing (T3, T4, ultrasensitive thyroid-stimulating hormone [TSH]; antibodies for thyroglobulin and microsomes) may be considered in anyone with a palpable goiter, family history of thyroid disease, or evidence of thyroid dysfunction (18). In some cases of chronic idiopathic/spontaneous urticaria that are not responsive to usual treatment, an ASST or an *in vitro* test for histamine release may be considered to determine the presence of functional autoantibodies before initiating immunomodulatory therapy; however, these tests are unlikely to change treatment outcomes.

A CBC (to rule out anemia, leukocytosis, or eosinophilia), TSH, urinalysis, and transaminases are the most likely tests to demonstrate significant abnormalities. The sedimentation rate may be elevated in active vasculitis. Circulating hepatitis-related antibodies may indicate acute or chronic disease. Complement studies, as previously discussed, are important to the diagnosis of hereditary and acquired angioedema and can be useful in difficult to control cases. Because the incidence of a false-positive antinuclear antibody can be as

high as 30% in patients with chronic idiopathic/spontaneous urticaria, it is not recommended in the absence of symptoms of underlying autoimmune disease (112).

Skin biopsy is currently suggested for chronic idiopathic/spontaneous urticaria that is difficult to manage, and it is probably indicated in patients with autoimmune disease or a complement abnormality. Acute urticaria usually does not warrant biopsy when laboratory studies are normal.

Therapy

Pharmacologic therapy is the main form of treatment for urticaria and angioedema (Table 31.7). However, as in other forms of allergic disease, if an allergen or a specific trigger has been identified, avoidance is the most effective treatment. For most urticaria patients, antihistamines are adequate to control symptoms, although for more severe acute flares, a short course of systemic corticosteroids may be required.

TABLE 31.7 STEPWISE TREATMENT OF CHRONIC IDIOPATHIC/SPONTANEOUS URTICARIA

Avoidance of triggers

Monotherapy with second-generation H_1 antihistamine

Increase dose of or add an additional second-generation H_1 antihistamine

Add first-generation H_1 antihistamine at bedtime

Add leukotriene receptor antagonist

Add doxepin

Add ketotifen if available

Increase antihistamine doses

Cautious short-term use of corticosteroids

Add omalizumab

Consider adding other anti-inflammatory or immunomodulating agents (cyclosporine, sulfasalazine, tacrolimus, colchicine, and hydroxychloriquine)

Sympathomimetic agents, notably epinephrine, have α agonist properties that cause vasoconstriction in superficial cutaneous and mucosal surfaces, which directly opposes the effect of histamine on these end organs. It should be prescribed and used for patients with a history of episodes of life-threatening angioedema.

H_1 antihistamines are the mainstay of symptomatic improvement or control of urticaria and angioedema. They have been thought of as competitive inhibitors of histamine, reducing the end-organ effect of histamine even if histamine release continues. Recent experiments have demonstrated that the H_1 antagonists actually are "inverse agonists" of the H_1 receptor and decrease the H_1 response in the absence of the agonist histamine (113). Second-generation antihistamines offer some valuable options because they are long-acting, cause little sedation, and are free of anticholinergic effects. Fexofenadine (114), cetirizine (115) levocetirizine (116), and desloratidine (117) are well tolerated and effective in most cases of chronic urticaria. Ketotifen (118) is another effective alternative for the treatment of chronic urticaria and physical/inducible urticarias because, in addition to being a histamine antagonist, it can inhibit mast cell degranulation (119). While the oral formulation is currently not on the market in the United States, ketotifen is available in 2-mg tablets in many countries. Low-dose doxepin, a tricyclic antidepressant, is unique in having very potent H_1 and H_2 antagonist effects and inhibits other mediators, such as platelet-activating factor (120). The main side effect is sedation, but when administered in small doses (10 to 30 mg) at bedtime, this may be avoided. A trial of therapy with representative agents from the different classes of antihistamines may be required to select the proper drug.

A stepwise approach to controlling urticaria is recommended by both American and European guidelines. If a single second-generation antihistamine is not adequate, using a combination of second-generation antihistamines or increasing one agent to up to four times licensed dosages has been shown to be effective and safe in 75% of patients with difficult to control urticaria (121). Additionally, an effort should be made to determine what period of the day each patient is most symptomatic (usually evening or early morning) to maximize therapy at that time. In addition, or alternatively, leukotriene modifiers such as montelukast and zileuton have been reported to help control chronic urticaria as well as reduce corticosteroid requirements in an undefined small subset of patients (122,123). These agents work best when given in combination with antihistamines. Limited benefit has been reported from using H_2 antihistamines

for both acute and chronic urticaria.

Corticosteroids, such as oral prednisone, used in combination with antihistamines may be necessary in the management of urticaria. Because of their potential for significant long-term side effects, these drugs should be used to control urticaria only after a demonstrated failure of both high-dose and combination antihistamine therapy. Based on clinical experience, moderate-dose steroid therapy (30 to 40 mg prednisone) may be required initially to control the urticaria. Thereafter, alternate-day therapy generally provides control on a long-term basis, often with decreasing doses. As in all forms of therapy, the risk to benefit ratio must be assessed when using steroid therapy for long-term treatment. Short-term prednisone has limited side effects, and is often useful for control of severe acute urticaria not responding to antihistamines. DPU frequently may require the use of low-dose or alternate-day corticosteroids to maintain the patient's activity, and a cautious trial of an NSAID may be helpful.

The choice of agents and the route of administration of drugs are dependent on the clinical situation. The adult patient who presents in an emergency room or physician's office within hours of the onset of life-threatening angioedema or severe urticaria can be treated with epinephrine 0.3 mL (1:1,000) intramuscularly, as well as hydroxyzine 25 to 50 mg or cetirizine 10 mg orally. Such an approach gives prompt relief from symptoms in many patients. After evaluation for a precipitating agent (e.g., drug or food), the patient may be released with instructions to take hydroxyzine or cetirizine for 24 to 48 hours. A brief burst of corticosteroids and prolonged observation may be judicious, and is essential if there have been associated signs of anaphylaxis. Ambulatory medical follow-up should be required.

The patient who presents with urticaria of several days' duration may be treated with regular doses of antihistamines. The combination of cetirizine 10 mg every morning and hydroxyzine 25 mg at bedtime is quite useful. Leukotriene modifiers, oral albuterol, or doxepin antagonist may be prescribed with the initial antihistamine. Failure to respond in a few days to this therapy may indicate the need for a short course of prednisone. Many patients respond to this therapy, but the antihistamines should be continued for a period after the prednisone is stopped.

The patient with a history of chronic urticaria presents a more complicated therapeutic problem. Following evaluation for an etiology, therapy is usually initiated in the stepwise manner described above and in Table 31.7, often a combination of levocetirizine, fexofenadine, cetirizine, hydroxyzine, or doxepin

and, possibly, a leukotriene modifier. Failure to respond suggests that moderate-dose prednisone should be initiated if the symptoms are sufficiently severe. Every effort to use alternate-day therapy should be made, but this is often initially inadequate. When control is achieved, the steroids are slowly withdrawn. For those patients who are unable to discontinue corticosteroid therapy, use of a steroid-sparing agent should be considered. In March 2014, the Food and Drug Administration approved the use of omalizumab at doses of 150 or 300 mg subcutaneously every 4 weeks for patients with chronic urticaria not controlled by H_1 antihistamines. The majority of patients have a rapid response to omalizumab, with improvement within 1 week of their first dose, whereas others average a time to response of 12 weeks (124–126). Although it is effective in both spontaneous and inducible forms of chronic urticaria, the mechanism of action of omalizumab remains unclear, and none of the current theories, such as downregulation of IgE receptors, reduction of mast cell releasability, reversal of basopenia, reduction of IgG autoantibodies against FcεRI and IgE, or decreasing the role of coagulation, can fully explain its efficacy (127). The ideal duration of therapy has yet to be determined such that once control is achieved, the dosing frequency should be adjusted on an individual basis taking into consideration the severity and duration of chronic urticaria as well as response to therapy.

In refractory patients thought to have CAU with the presence of functional antibodies, low-dose cyclosporine (2.5 mg/kg/day) given for 3 to 4 months has been shown to be effective and safe (128,129); however, blood pressure, renal function, as well as serum lipids need to be monitored throughout treatment.

Other anti-inflammatory medications have been reported in small studies or case reports to be useful in refractory patients (130). Hydroxychloroquine (131), dapsone (132), colchicines (133), and other immunomodulatory drugs, including methotrexate (134), tacrolimus (135), and mycophenolate mofetil (136), have been used experimentally for chronic urticaria. Sulfasalazine has been reported to be effective for DPU as well as other chronic urticaria (137,138).

Patients with urticaria can be very uncomfortable, have difficulty sleeping, and sometimes avoid social/work situations because of cosmetic appearance. Aggressive and consistent therapy for at least several months provides relief in many cases. Every effort should be made to find the best regimen with the least amount of side effects to control their symptoms.

In summary, urticaria may be unpleasant, frustrating, and frightening to a patient. Often, these patients seek help from various physicians for an allergen that does not exist. At times, they undergo expensive, inappropriate tests, and

treatments that are of no value and perhaps dangerous. These patients need reassurance. Although the duration of chronic idiopathic/spontaneous urticarial is highly variable, tailored treatment will most often induce remission.

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Approach to the Patient with Pruritus

BARRY LADIZINSKI AND DAVID C. REID

■ INTRODUCTION

Pruritus, or itching, is a common, complex, and often debilitating sensation that, if sufficiently intense, can provoke conscious or reflex scratching, or the desire to scratch. The word, *pruritus*, originates from the Latin prurire (to itch). The suffix "itus" is not to be confused with the Greek-derived "itis," meaning "inflammation of." While the temporary discomfort of itch, such as that which develops after an insect bite, is common, pruritus that is generalized, severe, or persistent can be incapacitating and suggestive of internal disease.

Itching is the most commonly reported dermatologic symptom. When it is symptomatic of a visible skin problem, the etiology may be discerned from physical examination or biopsy. Pruritus in the absence of cutaneous findings, however, is a diagnostic challenge, and effective therapy may be elusive. This chapter begins with an overview of pruritus and then discusses the investigation and management of itching in the absence of skin disease.

■ CLASSIFICATION

There is no universally accepted classification of pruritus, and nomenclature is variable. Generally, itching is described as "cutaneous" (due to skin disease) or "essential" (lacking skin findings). It may also be distinguished based on source: dermatologic or pruritoceptive (originating in the skin due to localized irritation), systemic (arising from pathology in internal organs), neurogenic/neuropathic (due to diseases of the central or peripheral nervous system), and psychogenic (due to psychiatric disease).

In 2007, the International Forum for the Study of Itch formed a clinically based classification of pruritic diseases (1):

1. Pruritus on diseased (inflamed) skin.

2. Pruritus on nondiseased (noninflamed) skin.

3. Pruritus with severe secondarily scratched lesions.

This chapter focuses on group II. It is important to note, however, that the presence of skin findings does not exclude an underlying systemic cause, and the absence of skin eruption does not equate with systemic disease.

PATHOPHYSIOLOGY

It was long believed that nociceptors in the skin mediate both pruritus (through weak activation) and pain (through stronger activation), but more recent evidence suggests that specific receptors and nerves selectively signal itch. The triggering sensation is transmitted by a functionally distinct subset of afferent, unmyelinated C-fibers (2). These neurons respond to histamine, interleukin-2, μ- and κ-opioid system changes, and substance P (SP) (3). They are insensitive to mechanical stimuli. Different receptors may be responsible for itching resulting from electrical stimuli or friction. After reaching dorsal horn neurons in the spinal cord, the stimulus travels to the thalamus and cerebral cortex, producing the itch sensation and, through activation of the motor cortex, the desire to scratch.

ETIOLOGY

Itching without skin lesions may be because of underlying systemic disease, result from a neuropsychiatric disorder, or be an adverse effect of pharmacologic therapy. In all, 10% to 50% of patients with pruritus have an underlying systemic disease—chronic renal disease, cholestasis, hematologic malignancies, thyroid dysfunction, HIV infection, and carcinoid syndrome being the most common (4).

HISTORY

A detailed history is essential to elucidate the etiology of itching. In cases without visible skin findings, temporal associations, environmental factors, and systemic symptoms can be important diagnostic clues. No particular clinical characteristic helps define the probability of an underlying disease, but some prediction can be made from the summation of features. Sometimes, multiple office visits and review of patient self-kept journals are necessary.

TABLE 32.1 MEDICAL HISTORY QUESTIONS FOR THE PRURITIC PATIENT

- **Distribution:** generalized, localized, acral (cholestasis)

Leading questions are suggested in Table 32.1. Abrupt onset of severe itching is uncommon for systemic disease, which usually presents insidiously. Systemic diseases often produce generalized, symmetric itching, whereas a localized distribution suggests a neuropathic etiology, such as brachioradial pruritus (5) or notalgia paresthetica. Prior to direct questioning, the patient may not realize that itching occurs at specific times of day or is related to particular activities, such as bathing or exercise. Itching is typically more problematic at night, so this diurnal variation is of limited diagnostic value.

The feeling of insects crawling or biting under the skin is called formication, and may be a symptom of depression or a side effect of certain drugs. However, the presence of a psychologically localized, fixed, immutable belief that the discomfort stems from infestation, despite a lack of objective evidence, portends the condition, delusions of parasitosis or delusional infestation. A telltale sign is the appearance in the doctor's office of small bags or boxes of lint, skin flakes, and textile fibers for microscopic examination, known as the "matchbox sign" or "Ziploc bag sign." Delusions of parasitosis is related to Morgellons disease (6).

Medications known to cause or worsen pruritus are listed in Table 32.2. Interestingly, some drugs known to exacerbate itching in one situation may relieve the symptom in another. These include aspirin, used together with paroxetine for pruritus associated with polycythemia vera (7,8), and indomethacin, sometimes helpful for HIV-associated pruritus (9).

The review of systems may help uncover systemic illness. Fever, weight loss, and fatigue may suggest malignancy, such as lymphoma. Common symptoms of

thyroid disease include heat or cold intolerance, diarrhea or constipation, and hair loss or change. Neurologic symptoms in the presence of paroxysmal pruritus may be a clue to multiple sclerosis (10). Information about sexual behavior, use of illicit substances, blood transfusions, personal living situations, and travel may lead to early identification of infections and infestations.

◾ PHYSICAL EXAMINATION

In most cases of itching, an obvious primary skin disorder, such as atopic dermatitis, urticaria, or arthropod reaction, will be manifest. The absence of readily visible findings does not exclude the possibility of a primary cutaneous cause. Xerosis and scabies, for example, can be easily overlooked; careful inspection is required to identify fine scaling and papules, and burrows, respectively. Dermoscopy can be utilized to confirm the presence of organisms (11), or lack thereof (12). Because urticaria is intermittent, wheals are often absent during an office physical exam. However, the presence of dermatographism, which can be elicited by firmly stroking the patient's skin with a tongue blade, helps suggest the diagnosis. Active cutaneous fibrosis in systemic sclerosis is often itchy, and the skin may appear smooth and tight. It is important not to mistake excoriations, prurigo nodules, or lichenification (thickened skin with increased skin markings) for primary cutaneous findings. These secondary lesions result from chronic rubbing, picking, or scratching. Given the transient or episodic nature of some cutaneous diseases, re-examination over time may lead to diagnostic findings.

TABLE 32.2 COMMON SYSTEMIC CAUSES OF GENERALIZED PRURITUS
CHRONIC RENAL FAILURE
HEPATIC CHOLESTASIS (OBSTRUCTIVE HEPATIC DISEASE OF ALL TYPES)
• Primary biliary cirrhosis
• Primary sclerosing cholangitis
• Choledocolithiasis
• Bile duct carcinoma

- Viral hepatitis

- Drug-induced hepatitis

- Pregnancy-associated cholestasis

ENDOCRINE

- Functional thyroid or parathyroid disorder

MALIGNANCY

- Hodgkin disease

- Non-Hodgkin lymphoma

- Myeloid and lymphatic leukemia

- Myelodysplasia

- Solid tumors, carcinoid tumors

HEMATOLOGIC

- Polycythemia vera

- Paraproteinemia

- Mastocytosis

PHARMACOLOGIC

- Chloroquine, clonidine, gold, lithium, β-blockers, tamoxifen, captopril, sulfonamides, retinoids, tramadol, aspirin, nonsteroidal anti-inflammatory agents, codeine, cocaine, morphine, hydroxyethyl starch[a]

PSYCHOGENIC

- Depression

- Generalized anxiety disorder

- Obsessive compulsive disorder

- Delusions of parasitosis

NEUROLOGIC

- Notalgia paresthetica

- Brachioradial pruritus

- Postherpetic neuralgia

[a]Hydroxyethyl starch is a component of colloid plasma volume expanders (70).

To identify systemic disease, a standard physical examination is helpful, including assessments for cachexia, pallor, jaundice, palpable lymph nodes, and enlargement of the liver or spleen. Examination of the nails may reveal findings, such as half and half nails (renal disease), Terry white nails (hepatic disease or endocrinopathy), koilonychia (iron deficiency anemia), or distal onycholysis (hyperthyroidism). System-specific signs are detailed in section "Pruritus in Systemic Disease."

LABORATORY AND IMAGING STUDIES

Screening laboratory tests may not be necessary at initial presentation. If the history and physical examination do not suggest a systemic disease, a trial of antipruritic therapy is reasonable (see section "Treatment"). Ongoing itching that

is nonresponsive to such therapy should lead to investigation for systemic disease (see Table 32.3).

A skin biopsy may occasionally help evaluate for underlying skin diseases that can have subtle physical findings, such as cutaneous mastocytosis. However, in the absence of clinically apparent disease, a skin biopsy should be avoided to prevent overdiagnosis, such as the finding of dermal mast cells without other evidence supporting mastocytosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for systemic causes of generalized pruritus is broad, including conditions affecting the hepatic, renal, hematologic, and endocrine systems. Several malignancies and drugs are known to induce pruritus, and neurologic and psychogenic disorders must also be considered. The most common underlying disorders are listed in Table 32.2.

TREATMENT

Despite recent advances, therapy is often frustrating. Clinical studies assessing efficacy are difficult to interpret, because the placebo effect ranges from 50% to 66% (13). Often, therapy specific for the particular systemic disease is highly effective. Reduction of stress and anxiety, as well as physical exercise and relaxation techniques, may also be beneficial.

Topical Therapy

The use of appropriate topical therapy, together with avoidance of scratching and rubbing, is crucial. Strict behavior modification to avoid manual manipulation and encouraging frequent (at least daily) application of emollients are essential. Bathing, showering, and use of soap often aggravate itching, even when there is a systemic cause. Occlusive agents, such as petrolatum, mineral oil, and lanolin, act as barriers to decrease water loss from the skin. Glycerin, urea, and α-hydroxy acids are types of humectants, which help deliver water to the stratum corneum. Newer moisturizers contain ceramide, a natural component of the skin's lipid bilayer, which enhances hydration. Thick, greasy products are generally the most effective, but the unpleasing texture and appearance may affect patient compliance, so combination regimens may be better tolerated, such as the use of a nonoily cream during the day and a thicker messier ointment at night. Application of emollient after bathing while the skin is still damp helps prevent xerosis of the stratum corneum caused by water evaporation.

TABLE 32.3 SUGGESTED LABORATORY EVALUATION FOR GENERALIZED PRURITUS OF UNKNOWN ORIGIN

Recommended

- Complete blood count, including differential

- Chemistry profile, with blood urea nitrogen, creatinine, and fasting glucose

- Liver function: transaminases, alkaline phosphatase, total and direct bilirubin, γ-glutamyl transpeptidase

- Thyroid function: thyroid-stimulating hormone; if abnormal, thyroxine (T_4) and triiodothyronine (T_3)

- Erythrocyte sedimentation rate, C-reactive protein

Optional (as indicated by results of above or from examination)

- Chest X-ray

- Stool examination for ova, parasites, occult blood

- Human immunodeficiency virus testing

- Viral hepatitis testing

- Parathyroid function: parathyroid hormone, calcium, phosphate

- Serum tryptase, 24-h urine histamine

- Serum protein electrophoresis with immunofixation

- Urine protein electrophoresis with immunofixation

- Abdominal ultrasound/CT scan

- Iron studies: serum iron, serum ferritin, transferrin (total iron binding capacity)

- Skin biopsy is rarely helpful and may cause diagnostic confusion

CT, computed tomography.

Other mainstays of topical treatment include cooling counterirritants (menthol, phenol, or camphor) or topical anesthetics (lidocaine or pramoxine). Capsaicin, a naturally occurring alkaloid found in chili peppers, activates the transient release potential vanilloid-1, which initially induces release of SP from peripheral sensory neurons, producing a burning pain. Repeated application, however, depletes SP and prevents its reaccumulation, thus reducing pruritus (14). A topical formulation of naltrexone, an opioid receptor antagonist that modifies epidermal μ-opiate receptor expression, has also been shown to decrease pruritus (15). Topical diphenhydramine should be avoided related to a high risk of sensitization, and topical doxepin can be problematic owing to potential systemic side effects. Recently, a combination of compounded topical ketamine and amitriptyline has been associated with improvement in neuropathic itch associated with brachioradial pruritus (16) and herpes zoster (17).

Topical steroids can help disrupt the itch–scratch cycle that exacerbates eczema or lichenification, but should be used only in the presence of skin inflammation, and not indiscriminately. Moderate potency steroids, such as triamcinolone acetonide 0.1% ointment, are reserved for the trunk and extremities, whereas more mild agents, like 1% hydrocortisone cream, are appropriate for the face, groin, or axilla, where skin is thin and more prone to atrophy. Topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus) are immunomodulating agents that exhibit comparable efficacy to mild corticosteroids (18). They often cause temporary burning skin discomfort, but lack the long-term adverse effects of steroids.

Systemic Therapy

H_1 antihistamines are often used to control the pruritus associated with urticaria, a histamine-mediated problem. However, when used to control itch without other skin manifestations, the main effect is probably soporific rather than truly

antipruritic (19). Consequently, first-generation, sedating, H_1 antihistamines may be used, but H_2 and H_3 antagonists are not indicated.

μ-Opioid receptor antagonists, such as the orally administered naltrexone, have been used for generalized itching due to both dermatologic and systemic causes (20), but are most useful for cholestatic pruritus (21,22). Naloxone infusions can be used for acute exacerbations (23). Recently, the κ-opioid receptor agonists, butorphanol (24) and nalfurine (25), have been used to treat intractable pruritus.

Gabapentin and its successor, pregabalin, structural analogs of γ-aminobutyric acid, modulate central nervous system pathways of itch and pain. Titrated slowly upward, they may be helpful for chronic pruritus (26).

Of the selective serotonin reuptake inhibitors, only paroxetine has been shown to improve pruritus related to systemic disease (27,28), suggesting its benefit may be elicited through a nonserotoninergic mechanism. Nausea is common, and abrupt cessation can cause severe pruritus and acute anxiety. Mirtazapine, a tetracyclic antidepressant that works centrally by increasing release of norepinephrine and serotonin, is also an antagonist of serotonin, H_1 histamine, peripheral α_1-adrenergic, and muscarinic antagonist receptors. It may be especially helpful for difficult cases of nocturnal pruritus because sedation is a commonly reported side effect (29).

Rarely, thalidomide, a tumor necrosis factor-α inhibitor and immune modulator, may be used, but its utility is limited by the almost universal development of peripheral neuropathy. Cholestyramine, an anion-exchange resin that binds bile acids in the gastrointestinal tract, thus interrupting their enterohepatic circulation, has been used for many years to relieve cholestatic pruritus (30,31), but currently, rifampin, a hepatic enzyme inducer, is considered first-line therapy (32–34). The typical antipsychotic pimozide, and more recently the atypicals olanzapine, risperidone, and aripiprazole, have been used for delusions of parasitosis or delusional infestation (35–38).

Broadband or narrowband ultraviolet light B (UVB) therapy, typically given for a few minutes three times weekly, is considered the treatment of choice for renal pruritus (39), and has shown efficacy in cholestatic pruritus, aquagenic pruritus, HIV-associated pruritus, and polycythemia vera (40). UVB therapy decreases dermal mast cells (41), presumably through inducing apoptosis (42), and can induce remission in as few as six to eight treatments (43).

Given the association of pruritus and stress-related mediators, it is not

surprising that psychologic approaches reduce itch intensity. Behavioral therapy, biofeedback, and alternative therapies, such as acupuncture or acupressure, may improve symptoms and quality of life (44,45).

PRURITUS IN SYSTEMIC DISEASE

Although there are few definitive associations between particular symptoms or signs and specific systemic causes of pruritus, some associations may be inferred.

Pruritus and Renal Disease (Uremic Pruritus)

At least 30 to 90% of chronic renal failure patients suffer from ongoing itch (46). In contrast, acute renal failure rarely causes pruritus, suggesting that, as with other uremic symptoms, elevated serum urea or creatinine is not causative. Instead, elevated levels of histamine, serotonin, and divalent ions, such as calcium, phosphate, magnesium, and aluminum, as well as imbalance of the μ- and κ-opioid receptors on lymphocytes have been implicated. In addition, uremic patients with pruritus have more dermal degranulated mast cells than those without itch (47,48). The initiation of dialysis does not necessarily alleviate pruritus, presumably because there is some persistent solute retention (49). For unknown reasons, those on hemodialysis are more often affected than those on continuous ambulatory peritoneal dialysis (4). The involvement of immunologic dysfunction is inferred from the absence of itch in those with a poorly functioning transplanted kidney until such time as immunosuppression is discontinued. Nephrogenic systemic fibrosis, a rare condition that affects patients with end-stage renal disease (glomerular filtration rate < 30 mL/min/1.73 m$_2$) and a history of gadolinium-containing contrast agent exposure, can be very itchy during early stages of active fibrosis (50).

Renal pruritus is an independent marker for mortality (51,52), possibly related to the negative impact on sleep quality. It is typically chronic (lasting 6 months or longer), and frequent, with nearly 50% of patients experiencing daily symptoms (46). The distribution is usually symmetric and generalized, but symptoms can be localized to the back, abdomen, scalp, or shunt arms (46,53). The itch intensity may increase during nighttime, summer months, or immediately following hemodialysis sessions. On physical examination, xerosis, decreased mental acuity (suggestive of uremia), and peripheral neuropathy may be evident.

Pruritus and Liver Disease (Cholestatic Pruritus)

Cholestatic itching is related to impaired bile secretion and occurs with all types of obstructive liver disease (54) (see Table 32.2). Although intracutaneous injections of bile acids produce pruritus (55), the deposition of bile salts in the skin is not, as once believed, the causative factor. In actuality, the causative factors include elevated histamine levels, accumulation of pruritogenic intermediates in bile salt synthesis, and the release of pruritogenic substances (e.g., opioid receptors) from injured liver cells, epidermal cells, and macrophages (56). Seventy percent of patients with primary biliary cirrhosis suffer from itching (57), and pruritus is often the presenting symptom. The spontaneous disappearance of pruritus in patients with hepatitis may signify a severe deterioration in hepatic function with a parallel worsening of prognosis (58). Itching associated with liver disease is insidious in onset, mild in severity, and begins acrally, with subsequent progression to generalized involvement. Hot spots on the hands and feet, or on areas restricted by tight-fitting clothing, may persist. Only rarely are the head, neck, or genitalia involved. Scratching does not relieve the sensation, and patients may scratch until they bleed, producing linear erosions (excoriations) (59).

The stigmata of liver failure seen on physical examination are well established and include icterus, ascites, dilated abdominal wall vessels (caput medusae), purpura, palmar erythema, spider angiomas, gynecomastia, small muscle wasting, Dupuytren contractures, and hepatosplenomegaly.

Malignancy-Associated Pruritus

Solid malignancies are infrequently associated with pruritus. Gastric carcinoids, through serotonin release, produce itchy episodes of intense flushing. In other cases of solid malignancy, the dorsal arms and anterior legs are preferentially affected. Specific tumors may be associated with localized itching—as with brain tumors presenting with nostril itching, for example (60). However, a full investigation for solid tumors in patients with generalized pruritus is not warranted, because the incidence of solid malignancies is the same as in the general population (61).

TABLE 32.4 **THERAPIES FOR GENERALIZED PRURITUS**
PHARMACOLOGIC
Topical: emollients, menthol, phenol, eucalyptus, calamine, capsaicin, pramoxine, doxepin, naltrexone

Oral

Sedating antihistamines: H_1 only

Opiate antagonists: naltrexone, naloxone

Neurologic: gabapentin, pregabalin

Psychiatric: mirtazapine, paroxetine

Immunomodulatory: thalidomide

NONPHARMACOLOGIC

Phototherapy (narrowband UVB, broadband UVB, psoralen, and UVA)

Cognitive behavioral therapy, stress reduction, biofeedback

Acupuncture

Cutaneous field stimulation (localized pruritus only)

CAUSE-SPECIFIC

Renal Pruritus

UVB phototherapy (three times weekly)

Naltrexone (50–100 mg by mouth daily)

Gabapentin (200–300 mg after hemodialysis sessions)

Thalidomide (100 mg by mouth daily)

More common than solid tumors is the association of pruritus with hematologic malignancies, in particular Hodgkin lymphoma, leukemias, other lymphomas, and polycythemia vera. Severe, relentless itching, coupled with systemic symptoms (fever, chills, and night sweats) suggests lymphoma. Up to 30% of patients with Hodgkin lymphoma report pruritus, an important clue,

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because itching may precede diagnosis by up to five years (56). The distribution is usually generalized, although it can localize to areas draining the involved lymphatic channels. Occasionally, there is also a strong burning sensation.

Other itch-associated hematologic malignancies include non-Hodgkin lymphoma (10% of patients), cutaneous T-cell lymphoma, mastocytosis, multiple myeloma, and the leukemias (most often chronic lymphocytic leukemia). The pruritus of leukemia is typically milder than that of lymphoma. Recently, aprepitant, an oral neurokinin-1 receptor (NK-1R) antagonist, has demonstrated effectiveness in controlling refractory pruritus (62), particularly in patients with cutaneous T-cell lymphoma (63) and biologic cancer therapy–associated itch (64). Aprepitant exhibits its antipruritic properties by preventing binding of the NK-1R to its SP ligand, subsequently reducing SP levels that can contribute to itch (63,64).

Endocrine Pruritus

The excess thyroid hormone production in thyrotoxicosis leads to sympathetic overactivity, vasodilation, elevation of skin temperature, activation of kinin pathways, and lowering of the itch threshold, resulting in generalized pruritus in 4% to 11% of patients (65). Conversely, the itch of hypothyroidism, which affects up to 90% of patients, is not metabolic in origin, but related to xerosis. The hypothyroid individual may have coarse, thick, flaky skin, diffuse alopecia with thick brittle hair, ptosis, and loss of the lateral one-third of the eyebrows (Sign of Hertoghe or Queen-Anne's sign). The thyrotoxic patient may have smooth skin with hyperhidrosis, a fine tremor, diffuse telogen hair loss with thin hairs, proptosis, onycholysis, and, at times, urticaria.

Despite popular conception, generalized itching is not found more commonly in diabetics than in the general population (66), and with advanced peripheral neuropathy, all cutaneous sensations may be muted. Localized areas of itch may result from cutaneous candidiasis, lichen simplex chronicus, or nummular eczema.

Pruritus without Skin Signs Related to Infectious Disease

Pruritus may be the presenting sign of HIV infection. Severe itching occurs with progressive infection (CD4 count < 50 cells/mm^3), possibly through the effect of viral proteins on nociceptive neurons. Other signs of HIV are equally nonspecific, but include weight loss, seborrheic dermatitis, Kaposi sarcoma, and other coexisting infections (67).

Hematologic Pruritus

Itching occurs in up to 50% of patients with polycythemia vera and often predates the diagnosis by several years. The pruritus is characteristically aquagenic (i.e., an intense prickly itch occurs on contact with water of any temperature) (68), and a sudden drop in ambient temperature may produce similar symptoms. Plasma histamine, circulating basophils, and degranulated skin mast cells are increased (65). Physical examination may reveal splenomegaly, hepatomegaly, and plethora—a ruddy complexion in the face, mucosa, and conjunctiva. Despite previous reports, iron deficiency in the absence of other findings does not produce itch (69).

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CHAPTER 33

Antihistamines

JONATHAN A. BERNSTEIN AND TABI LESLIE

INTRODUCTION

Histamine, a low-molecular amine, is produced by the reaction of histidine decarboxylase on L-histidine (1,2). After its biosynthesis, this enzyme is located in cells found throughout the body, including the peripheral and central nervous system (CNS), gastric parietal cells, mast cells, and basophils (1–3). As a result of its ubiquitous presence in the body, it is not surprising that histamine has a wide range of biologic effects. Currently, it is known that histamine exerts these effects through four histamine receptors (HRs). Histamine is involved in sleeping and waking, energy and endocrine homeostasis, cognition and memory through histamine receptor 1 (H_1R), regulation of gastric acid secretion through H_2R, modulation of neurotransmitter release through H_3R, and facilitation of pro-inflammatory activities through H_4R (Table 33.1) (1). HR antagonists (antihistamines) can be categorized in terms of their structure, pharmacokinetics, pharmacodynamics, and clinical utility (Table 33.1) (1). Histamine binding to H_1Rs causes itching, pain, vasodilatation, vascular permeability, hypotension, flushing, headache, tachycardia, bronchoconstriction, stimulation of airway vagal afferent nerves and cough receptors, and decreased atrioventricular node

conduction time (1,2). Histamine binding to H_2Rs causes increased gastric acid secretion, vascular permeability, hypotension, flushing, headache, tachycardia, chronotropic and inotropic activity, bronchodilation, and airway mucus production (1,2). Histamine binding to H_3Rs prevents excessive bronchoconstriction and mediates pruritus through non–mast cell pathways (1,2). Finally, histamine binding to H_4Rs is important for differentiation of myeloblasts and promyelocytes. Histamine has been shown to have a number of immunomodulatory effects through these various receptors. Clinically, selective antagonists are available for blocking H_1 and H_2 receptors (Table 33.1) (1). Nonselective H_3- and H_4-receptor antagonists are available as research tools but not for clinical use at the present time, although their potential for therapeutic use is gradually being realized (Table 33.1) (1,4). Second-generation antihistamines, many of which have been derived from first-generation agents, are more selective for H_1Rs and have added a new dimension to the treatment of allergic disorders. Over the past several years, additional second-generation antihistamines have been introduced to the market and others, still under investigation may become available in the near future. This chapter provides an overview of the immunologic and clinical effects of histamine so that the reader can appreciate the evolving role of histamine antagonists in a broad spectrum of clinical disorders.

TABLE 33.1 CHARACTERISTICS OF HISTAMINE RECEPTORS

CHARACTERISTIC	H_1	H_2	H_3	H_4
Receptor described/human gene cloned	1966/1993	1972/1991	1983/1999	1994/2000
Best characterized function	Acute allergic reactions	Gastric acid secretion	Neurotransmitter modulation	Immunomodulator
Receptor proteins in humans	487 amino acids, 56 kD	359 amino acids, 40 kD	445 amino acids, 70 kD	390 amino acids
Chromosomal location in humans	3p25, 3p14-21	5q35.3	20q13.33	18q11.2

Receptor expression	Widespread (neurons, endothelial, smooth muscle)	Widespread (gastric parietal cells, smooth muscle, heart)	Histaminergic neurons	Bone marrow, peripheral hematopoietic cells (dendritic cells, mast cells, eosinophils, monocytes, basophils, and T cells)
G-protein coupling	$G\alpha_q$	$G\alpha_s$	$G\alpha_{i/o}$	$G\alpha_{i/o}$
Major signaling pathway	Increases in Ca^{2+}	Increases in cAMP	Inhibition of cAMP	Increases in Ca^{2+}
Histamine pK_i	4.2	4.3	7.8	8.1
Diphenhydramine pK_i	7.9	>10,000	<5	<5
Loratadine pK_i	6.8	ND	ND	<5
Cetirizine pK_i	8.0	ND	ND	<5
Fexofenadine pK_i	8.3	ND	ND	<5
Ranitidine pK_i	<4	7.1	<5	<5
Cimetidine pK_i	<5	6.2	<5	<5
Thioperamide pK_i	<5	<4	7.3	7.2
JNJ7777120 pK_i	<5	>4.5	5.3	8.4
Rupatadine	7.0	ND	ND	ND

Bilastine	7.37 ± 0.06	ND	ND	ND

THE DISCOVERY OF HISTAMINE AND HISTAMINE RECEPTORS: A HISTORIC PERSPECTIVE

Histamine or β-imidazolylethylamine was first synthesized by Windaus and Vogt in 1907 (5). The term *histamine* was adopted because of its prevalence in animal and human tissues (*hist*: relating to tissue) and its amine structure (Fig. 33.1) (6,7). Dale and Laidlaw (8) in 1910 were the first to report histamine's role in anaphylaxis when they observed a dramatic bronchospastic and vasodilatory effect in animals injected intravenously with this compound. Subsequently, histamine was found to be synthesized from L-histidine by L-histidine decarboxylase and metabolized by histamine *N*-methyltransferase to form *N*-methylhistidine or by diamine oxidase to form imidazole acetic acid (9). However, only the *N*-methyltransferase pathway is active in the CNS. Originally, histamine's classic physiologic actions of bronchoconstriction and vasodilation were believed to be responsible for the symptoms of allergic diseases through its action at one type of HR. In 1966, Ash and Schild (10) were the first to recognize that histamine-mediated reactions occurred through more than one receptor, based on observations that histamine had an array of actions, such as contraction of guinea pig ileal smooth muscle, inhibition of rat uterine contractions, and suppression of gastric acid secretion. This speculation was confirmed in 1972 by Black et al., (11) who used the experimental histamine antagonists, mepyramine and burimamide, to block histamine-induced reactions in animals. They observed that each of these antagonists inhibited different physiologic responses, suggesting that there were at least two HRs, now referred to as H$_1$ and H$_2$ (11). Arrang et al. (12) discovered a third HR (H$_3$) with unique physiologic properties, raising the possibility that additional, yet unrecognized, HRs exist. Table 33.1 summarizes the pharmacodynamic effects after activation

of the known HRs and their common agonists and antagonists (7,12,13). Characterizing HRs has been essential in discovering histamine's physiologic actions on target cells which include increased mucus secretion, increased nitrous oxide formation, endothelial cell contraction leading to increased vascular permeability, gastric acid secretion, bronchial relaxation, and suppressor T-cell stimulation. Finally, the H_4R was discovered based on a genomic approach using the H_3R sequence. As mentioned previously, this receptor is expressed more selectively on dendritic cells, mast cells, eosinophils, monocytes, basophils, and T cells; therefore, it is believed to have an important immunoregulatory role (14). Figure 33.1 illustrates the actions of histamine on HRs in allergic inflammation (15).
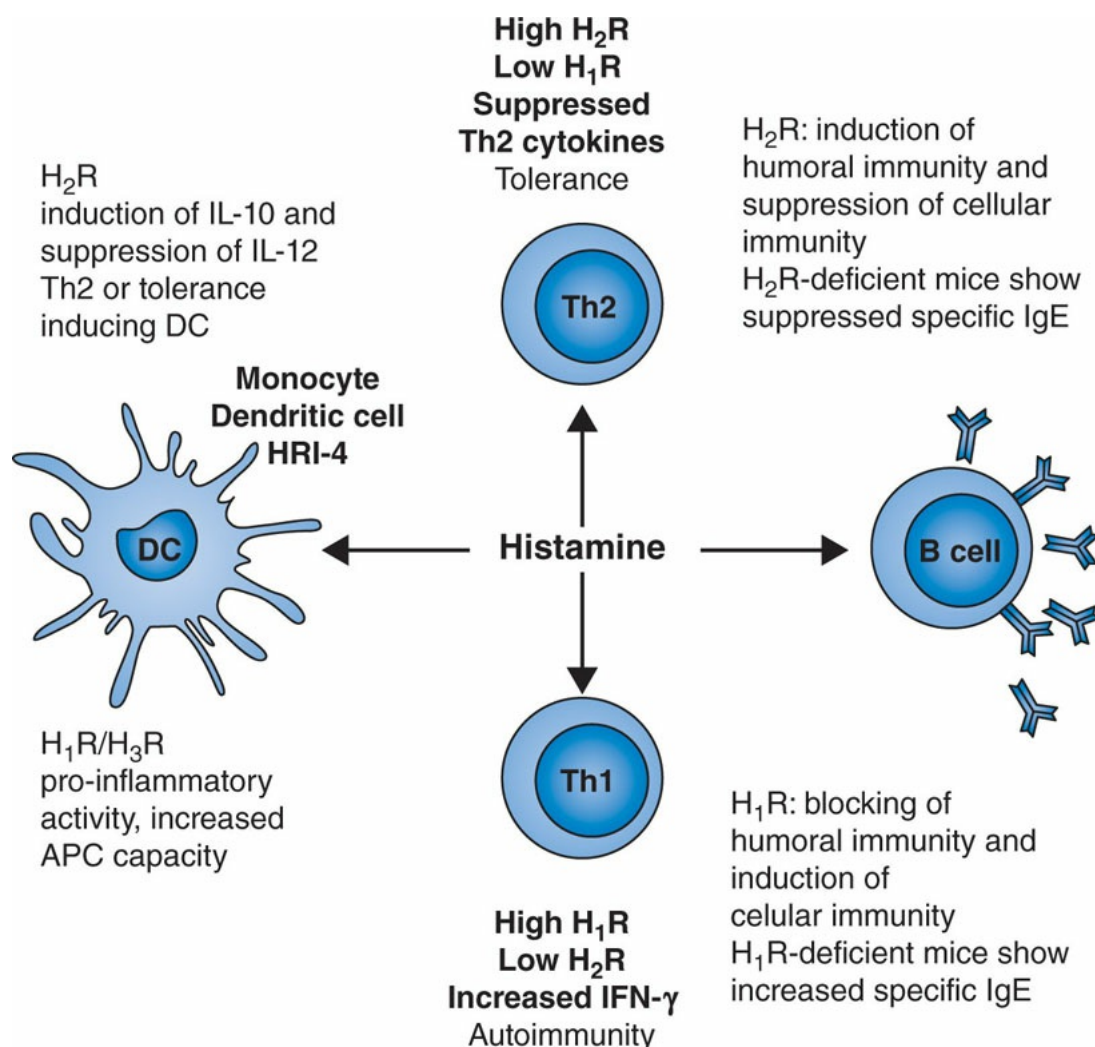
■ **FIGURE 33.1** Function of histamine on histamine receptors (HRs). APC, antigen-presenting cell; DC, dendritic cell; H_1R, histamine receptor 1; H_2R, histamine receptor 2; IFN-γ, Interferon-γ; IL, interleukin; IgE, immunoglobulin E. (Reproduced with permission from Simons FER, Simons KJ. The pharmacology and use of H_1-receptor antagonist drugs. *N Engl J Med.*

THE ROLE OF HISTAMINE IN ALLERGIC INFLAMMATION

Histamine is stored in the cytoplasm of mast cells and basophils, attached to anionic carboxylate and sulfate groups on secretory granules (15,16). Histamine is released from mast cell and basophil secretory granules after aggregation of high-affinity immunoglobulin E (IgE) receptors. IgE receptors are coupled to G-proteins which, when activated, lead to a sequence of chemical reactions with the end result being histamine release. However, histamine can be released spontaneously by activation of mast cells and basophils by histamine-releasing factors, which include chemokines (chemokine aka CCL5 [RANTES], monocyte chemoattractant protein–1 [MCP-1], and macrophage inflammatory protein 1α [MIP-1α]) and several cytokines (interleukin [IL]-1, IL-3, IL-5, IL-6, and IL-7) (9). Histamine can also be released when the MRGPRX2 is activated by various secretagogues, including peptidergic drugs.

Histamine's inflammatory action depends on which HRs are activated, the level of HR expression, and the effector cells involved (1,2). For example, H_1R expression is increased during the differentiation of monocytes to macrophages, and H_1R expression can be increased by a number of inflammatory stimuli (1,2,14,15). Furthermore, histamine has varying effects on different inflammatory cells. For example, mast cells express H_1, H_2, and H_4 receptors (1,2,14,15). Although histamine does not appear to have a direct effect on mast cell degranulation, by binding to H_4Rs, it can act synergistically with chemoattractants such as CXCL12 (1). In contrast, histamine binding to H_2 receptors on mast cells can act to inhibit histamine release and modulate cytokine production (1,2,15).

Low concentrations of histamine via H_4 receptors can induce eosinophil chemotaxis but at higher concentrations via H_2 receptors can attenuate this effect (1,2,16). Histamine binding to H_4 receptors can stimulate upregulation of adhesion molecules and reorganization of actin polymers, whereas binding to H_1 receptors can induce superoxide production and complement receptor upregulation in eosinophils (1,2,14,15).

Dendritic cells express H_1, H_2, and H_4 receptors (1,15). Histamine can cause chemotaxis of dendritic cells by binding primarily to H_4Rs and to a lesser extent

to H_1Rs (1). Furthermore, T-cell polarization may be regulated by histamine binding via H_1 and H_4 receptors on dendritic cells in conjunction with other chemokines, such as CCL17, thymus- and activation-regulated chemokine; CCL22; and CCL3 MIP-1α.

Histamine can have direct effects on T cells via H_1, H_2, and H_4 receptors which are expressed on CD4^{+} and CD8^{+} T cells (1). The effect of histamine on T-cell proliferation varies (1). It can increase T-cell proliferation by binding to H_1Rs and inhibit proliferation by binding to H_2Rs. Binding to H_2Rs has been demonstrated to inhibit T-cell production of IL-2, IL-4, IL-13, and interferon γ (1). However, the role of histamine in regulating T-cell proliferation is likely much more complicated than can be explained by the counterregulatory roles of cytokine production (1). More recently, it was shown that basophils express more H_4R mRNA than H_1R mRNA and that preincubation of basophils with histamine or the H_4R agonist ST-1006 resulted in decreased basophil activation and release of sulfidoleukotrienes in response to different FcεRI cross-linking stimuli (17).

H_1-RECEPTOR HISTAMINE ANTAGONISTS

First-Generation Agents

Structure

The first histamine antagonist was accidentally discovered in 1937 by Bovet and Staub who found that a drug originally being studied for its adrenergic antagonistic properties in guinea pigs also had potent antihistaminic activity (7). By 1942, safe and effective antihistamines developed for human use became available. Many of these agents, such as pyrilamine maleate, tripelennamine, and diphenhydramine, are still widely prescribed today (2,7).

The chemical structure of H_1-antagonists differs substantially from histamine (Fig. 33.2) (1). Histamine is composed of a single imidazole heterocyclic ring linked to an ethylamine group, whereas H_1 antagonists consist of one or two heterocyclic or aromatic rings joined to a "linkage atom" (nitrogen, oxygen, or carbon) (1,7). The linkage atom is important in structurally differentiating these groups of agents, whereas the number of alkyl substitutions and heterocyclic or aromatic rings determines their lipophilic nature (1,7). The ethylenediamines, phenothiazines, piperazines, and piperidines all contain nitrogen as their linkage atom, whereas the ethanolamines contain oxygen and the alkylamines contain

carbon as their linkage atoms (2,7).
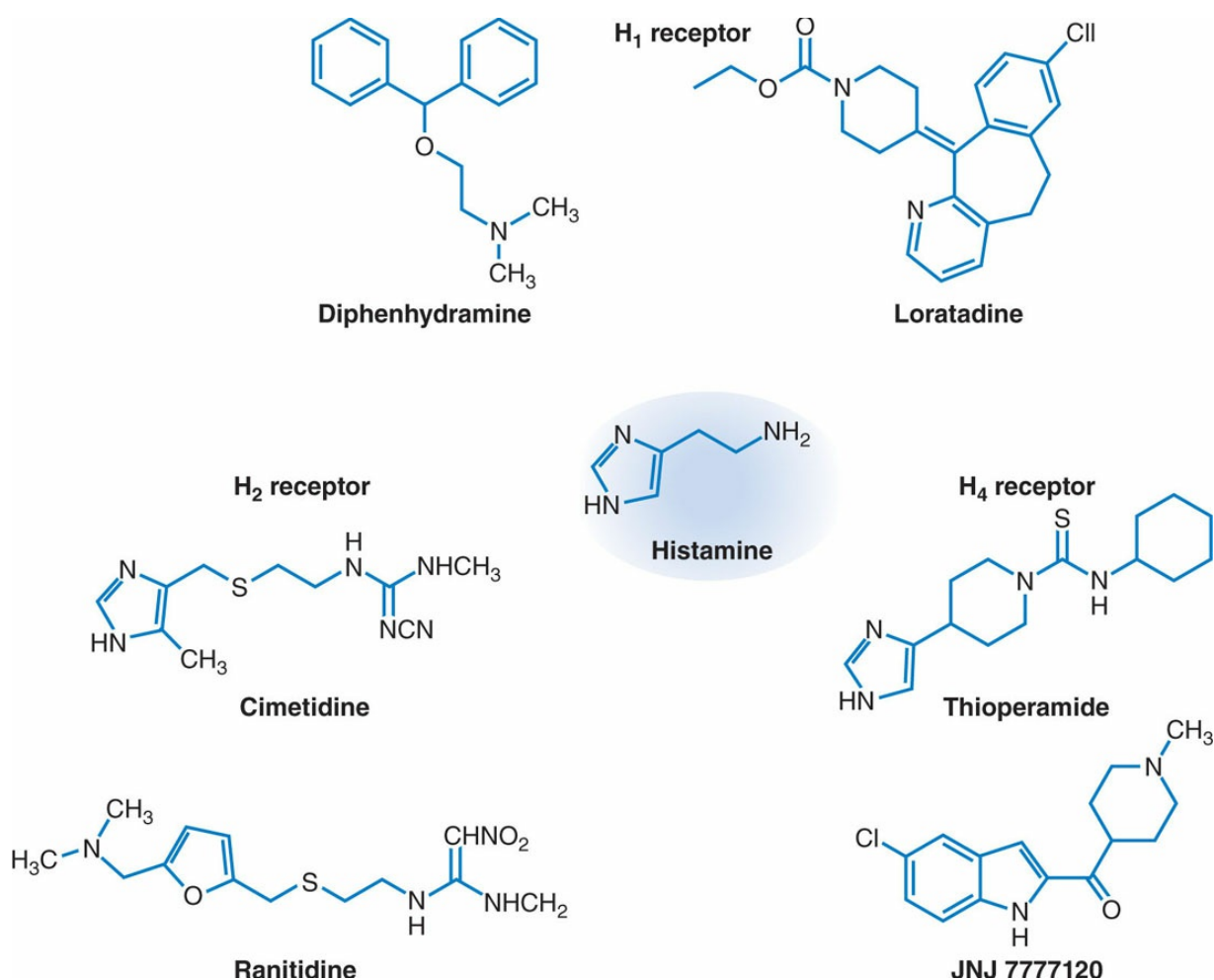
■ FIGURE 33.2 Structure of histamine and representative histamine receptor ligands. (Reproduced with permission from Thurmond RL, Glefand EW, Dunford PJ. The role of histamine H_1 and H_4 receptors in allergic inflammation: the search for new antihistamines. *Nat Rev Drug Discov*. 2008;7:41–53.)

Pharmacokinetics

Accurate pharmacokinetic data on first-generation antihistamines are now available in children and adults because of sensitive detection techniques, such as gas–liquid chromatography, mass spectrometry, and high-performance liquid chromatography (2,7,13). Generally, these compounds are rapidly absorbed orally or intravenously, resulting in peak serum concentrations within 2 to 3 hours and symptomatic relief within 30 minutes. They have large volumes of distribution, slow clearance rates, and are metabolized primarily by hydroxylation in the hepatic cytochrome P450 system. The vast majority of the parent drug is excreted as inactive metabolites in the urine within 24 hours of dosing. As a rule, serum half-lives ($t_{1/2}$) are longer in adults than they are for

children. Their lipophilic nature allows them to cross the placenta and the blood–brain barrier. This access into the CNS is responsible for many of the side effects experienced by patients. These agents are also excreted in breast milk (2,7,13). Table 33.2 summarizes pharmacokinetic and pharmacodynamic data for the most commonly used first- and second-generation agents (2,7,16).

Pharmacodynamics

The first-generation H_1 antagonists are thought to compete with histamine for binding to HRs. This competitive inhibition is believed to be reversible and, therefore, highly dependent on free drug plasma concentrations. Because these agents are metabolized and excreted into the urine as inactive metabolites, the HRs become desaturated, allowing surrounding histamine to bind. This mechanism emphasizes the need to instruct patients on using these agents on a regular basis to achieve a maximal therapeutic benefit (2,7,16). Experimental findings suggest another mechanism for the effects of H_1R antagonists. It has been speculated that H_1R antagonists are "inverse agonists," implying that they could decrease constitutive receptor responses (18). The H_1R antagonist is described as having "negative intrinsic activity," despite the release of histamine from mast cells or basophils.

TABLE 33.2 PHARMACOKINETICS AND PHARMACODYNAMICS OF ORAL H_1R-ANTAGONISTS IN HEALTHY YOUNG ADULTS

H_1R ANTAGONIST	T_{max}[a] SINGLE DOSE (h)	$T_{1/2}$ (HALF-LIFE)	% ELIMINATION UNCHANGED IN URINE/FECES	DRUG–DRUG INTERACTION	ONSET, DURATION OF ACTION(h)[b]	USUAL ADULT DOSE
First-Generation Drug (±SD)						
Chlorpheniramine	2.8 ± 0.8	27.9 ± 8.7	—	Possible	3, 24	4 to 12 su re to
Diphenhydramine						

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Drug						
	1.7 ± 1.0	9.2 ± 2.5	—	Possible	2, 12	25 up
Doxepin	2	13	—	Possible	—	25 up
Hydroxyzine	2.1 ± 0.4	20.0 ± 4.1	—	Possible	2, 24	25 up
Second-Generation Drug (±SD)						
Acrivastine	1.4 ± 0.4	1.4–3.1	59/0	Unlikely	1, 8	8
Cetirizine	1.0 ± 0.5	6.5–10	60/10	Unlikely	1, 24	5– qd
Loratadine (descarboethoxyloratadine)	1.2 ± 0.3 (1.5 ± 0.7)	7.8 ± 4.2 (24 ± 9.8)	Trace	Unlikely	2, 24	10
Fexofenadine	2.6	14.4	12/80	Unlikely	2, 24	60 bi m 18 qd
Desloratadine	1–3	27	0	Unlikely	2, 24	5
Levocetirizine	0.8 ± 0.5	7 ± 1.5	86/13	Unlikely	1, 24	5

Second-Generation Drugs Not Approved in the United States for Oral Use						
Ebastine (carebastine)	(2.6−5.7)(10.3–19.3)	(75–90/0)	—	2, 24	1(qd
Mizolastine	1.5	12.9	0.5/0	—	1, 24	1(
Rupatadine	0.75	5.9	0/0	Unlikely	2, 24	1(
Bilastine	1.3	14.5	33/67	Unlikely	1, >24	2(

Rupatadine from He SH, Zhang HY, Zeng XN, et al. Mast cells and basophils are essential for allergies: mechanisms of allergic inflammation and a proposed procedure for diagnosis. *Acta Pharmacol Sin*. 2013;34(10):1270–1283. Bilastine from Jones AW. Perspectives in drug development and clinical pharmacology: the discovery of histamine H_1 and H_2 antagonists. *Clin Pharmacol Drug Dev*. 2016;5(1):5–12.

[a]T_{max} denotes time from oral intake to peak plasma concentration.

[b]Onset and duration of action are based on wheal-and-flare studies.

bid, twice daily; H_1R, histamine receptor 1; qd, once daily; qid, four times daily; tid, three times daily.

From Thurmond RL, Glefand EW, Dunford PJ. The role of histamine H_1 and H_4 receptors in allergic inflammation: the search for new antihistamines. *Nat Rev Drug Discov*. 2008;7:41–53; Simons FE. Advances in H_1-antihistamines. *N Engl J Med*. 2004;351:2203–2217; and Simons FE. Antihistamines. In: Middleton E, Reed CE, Ellis EF, et al., eds. *Allergy Principles and Practice*. 5th ed. St Louis: CV Mosby, 1998:612–637.

Pharmacy

Table 33.3 summarizes the pediatric and adult dosing schedules of commonly prescribed antihistamines (13,16,19). Prior to the availability of pharmacokinetic data, these agents were believed to have short half-lives which necessitated frequent dosing intervals to be effective (18). Because chlorpheniramine, brompheniramine, and hydroxyzine have serum half-lives greater than 20 hours in adults, it may be feasible to administer these agents only once or twice a day to achieve similar efficacy. The availability of sustained-release preparations of shorter half-life agents has also allowed less frequent dosing, thereby improving patient compliance and minimizing side effects. It remains unclear whether treatment with sustained-released formulations of conventional agents with shorter half-lives offers any advantages over conventional agents with longer half-lives when dosed similarly (20).

Second-Generation Agents

Structure

The new H_1R selective, nonsedating class of antihistamines is categorized as second generation. Their structural and pharmacokinetic profiles are responsible for their milder side effects and better tolerance among patients (2,7). Fexofenadine, desloratadine, and loratadine are piperidines; cetirizine and levocetirizine are piperazines. Figure 33.1 lists the chemical derivations of these agents in addition to other similar compounds undergoing investigation, and Fig. 33.2 illustrates their structures in comparison to first-generation agents (2,7,13). The five currently available second-generation agents in the United States are fexofenadine, loratadine, desloratadine, cetirizine, and levocetirizine. Rupatadine, which is a highly selective H_1R antagonist with platelet-activating factor antagonism, is not available in the United States, but is approved in Europe for allergic rhinitis and urticaria. It has also been shown to significantly reduce the severity of itch in mosquito bite allergy and urticaria, as well as the pruritus associated with mastocytosis (21).

Terfenadine and astemizole are no longer available in the United States because of safety concerns. Both of these agents were associated with serious interactions with drugs that were also metabolized by the liver cytochrome P450 enzyme 3A4, such as erythromycin and ketoconazole. This led to accumulation of the parent compound, which caused cardiac side effects such as torsade de pointes (2,7). Although this was a rare occurrence and dose dependent, the advent of newer antihistamine drug metabolites that were not dependent on cytochrome oxidase metabolism made them expendable. Loratadine has not been

demonstrated to induce these cardiovascular side effects most likely because it is metabolized by two isoenzymes (CYP2D6 and CYP3A4) (22,23). Therefore, loratadine can be safely taken with macrolide antibiotics (e.g., erythromycin) and oral antifungal agents (e.g., ketoconazole) (22). It should be emphasized that terfenadine and astemizole were very safe and effective drugs which were able to be used in the vast majority of clinical circumstances. Cetirizine, fexofenadine, levocetirizine, or desloratadine do not affect the I_k or cause QTc prolongation (2).

Postsurveillance monitoring was essential for identifying these severe adverse cardiac effects of terfenadine and astemizole. As a result, we have gained a better appreciation for the roles of pharmacodynamics/pharmacokinetics and metabolism in drug development and pharmacoepidemiology (2,18). In fact, investigations into the adverse drug reactions associated with the second-generation agent, terfenadine, have served as prototypes for the design of current long-term surveillance studies monitoring the safety of drugs in a variety of clinical situations.

Pharmacokinetics

The pharmacokinetic data available for second-generation agents are summarized in comparison to first-generation agents in Table 33.2 (2,7,16,24). Fexofenadine, loratadine, and cetirizine are well absorbed from the gastrointestinal tract, with peak serum concentrations occurring within 1 to 2 hours after oral administration (2,7,16,24). Data on humans on volumes of distribution for these agents are not available (2,7,16).

Loratadine is metabolized by the cytochrome P450 CYP3A4 enzyme to form descarboethoxyloratadine. However, if the CYP3A4 enzyme is inhibited, loratadine can be alternatively metabolized by the CYP2D6 enzyme, thereby preventing increased levels of the unmetabolized parent compound. Astemizole undergoes oxidative dealkylation, aromatic hydroxylation, and glucuronidation through the P450-CYP3A4 pathway to form several metabolites (2). The major active metabolite of astemizole is *N*-desmethylastemizole which has a half-life of 9.5 days. Terfenadine is exclusively metabolized by oxidation and oxidative *N*-dealkylation through the P450-CYP3A4 pathway to form an active acid metabolite, fexofenadine and an inactive metabolite (MDL 4829), respectively (7).

TABLE 33.3 DOSAGES OF REPRESENTATIVE H$_1$R ANTAGONISTS

GENERIC NAME	ORAL DOSE (ADULTS AND CHILDREN 12–18 Y OF AGE)	ORAL DOSE (CHILDREN UNDER 12 Y OF AGE)
Non- or Low-Sedating Antihistamines		
Acrivastine	8 mg tid	Unlicensed
Bilastine (not available in the United States)	20 mg qd	Unlicensed
Cetirizine	10 mg qd	Unlicensed for use in children under 2 y 2–6 y: 2.5 mg tid 6–12 y: 5 mg tid
Desloratadine	5 mg qd	1–6 y: 1.25 mg qd 6–12 y: 2.5 mg qd
Fexofenadine	180 mg qd	6–12 y 30 mg bid
Loratadine	10 mg qd	2–12 y, <31 kg: 5 mg qd 2–12 y, >31 kg: 10 mg qd
Mizolastine	10 mg qd	Unlicensed
Rupatadine (not available in the United States or the United Kingdom)	10 mg qd	Unlicensed
Ebastine (not available in the United States or the United Kingdom)	10 mg qd	2–5 y, 2.5 mg qd 6–11 y, 5 mg qd

Sedating Antihistamines		
Alimemazine	10 mg bid/tid (max. 100 mg/d) Elderly: 10 mg qd/bid	6–24 mo: 250 µg/kg (max 2.5 µg tid/qid a day: specialist use only) Unlicensed for <2 y in the United Kingdom 2–5 y: 2.5 mg tid/qid 5–12 y: 5 mg tid/qid
Chlorphenamine	4 mg 4–6 hourly (max. 24 mg/d) Elderly: max. 12 mg/d	1–24 mo: 1 mg bid 2–6 y: 1 mg 4–6 hourly (max. 6 mg/d) 6–12 y: 2 mg 4–6 h (max. 12 mg/d)
Diphenhydramine (not available in the United Kingdom)	25–50 mg 4–6 hourly (max. 300 mg/d)	2–6 y: 6.25 mg 4–6 h 6–12 y: 12.5–25 mg 4–6 h (or 5 mg/kg or 150 mg/m^2: max. 300 mg daily)
Hydroxyzine	25 mg at night (up to 25 mg tid/qid) Elderly: up to 25 mg bid	6 mo–6 y: 5–15 mg in divided doses (max. 2 mg/kg daily) 6–12 y: 15–25 mg in divided doses (max. 2 mg/kg daily)
Promethazine	10–20 mg bid/tid	2–5 y: 5 mg bid (or 5–15 mg qd at night) 5–10 y: 5–10 mg bid (or 10–25 mg qd at night) >10 y: 10–20 mg bid (or 25 mg qd at night, up to 25 mg bid if necessary)

bid, twice daily; H_1R, histamine receptor 1; qd, once daily; qid, four times daily; tid, three times daily.

Adapted from Leslie TA, Grattan CEH. Antihistamines and related: H_1 antagonists,

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sodium cromoglycate, leukotriene receptor antagonists. In: Arden-Jones M, Hampton P, Vleugels R, eds. *Handbook of Dermatology Treatments: A Practical Guide to Topical Treatments, Systemic Therapies and Procedural Dermatology*. London: JP Medical; 2017.

Cetirizine and fexofenadine are not extensively metabolized in the cytochrome P450 system and are, therefore, less likely to compete for elimination with other medications metabolized by the same cytochrome P450 enzyme systems. Over 50% of cetirizine is eliminated unchanged in the urine. Its elimination can be impaired in patients with hepatic and renal insufficiency. Most of fexofenadine is eliminated unchanged in the urine and feces. Its elimination can also be impaired in patients with renal insufficiency (2,7).

Desloratadine, a metabolite of loratadine, is completely metabolized, whereas levocetirizine, the active enantiomer of cetirizine, is excreted unchanged 86% in the urine and 13% in the feces (2). Both drugs have low likelihood of drug–drug interactions but have to be dose adjusted in patients with renal and hepatic impairment (Table 33.2) (2).

Pharmacodynamics

In contrast to first-generation agents, second-generation agents do not operate by simple competitive inhibition. Instead, these agents bind to and dissociate from H_1 receptors slowly in a noncompetitive manner. They are not displaced from H_1Rs in the presence of high histamine concentrations (2). Although the second-generation antagonists are potent suppressors of the wheal-and-flare responses, this feature has not been established as a useful method for comparing the clinical potencies of the different agents currently available (25). Their lipophobic properties prevents them from crossing the blood–brain barrier, and thus their activity on H_1-receptors is restricted to the peripheral nervous system (2,26). They have very little affinity for non-H_1Rs (2,7).

Pharmacy

Second-generation antihistamines are only available as oral formulations (tablets and liquid). Cetirizine, chlorpheniramine, clemastine, cyproheptadine, diphenhydramine, desloratadine, and promethazine are available in solution or syrup form, and some can be administered parentally, although this may cause local irritation (27). All have convenient dosing once or twice daily (13,16). Studies have shown that a single dose of fexofenadine (180 mg) is equally effective as 60 mg twice a day at improving allergic rhinitis symptom scores and suppressing histamine-induced wheal-and-flare responses. All of the available

second-generation antihistamines have comparable antihistaminic potency; however, a head-to-head comparison study between levocetirizine and desloratadine using an environmental exposure unit reported that levocetirizine had a more rapid onset of action (1 versus 3 hours) and resulted in greater symptomatic relief after 24 hours compared to desloratadine (28).

DUAL-ACTION ANTIHISTAMINES

A number of agents currently not available for oral administration in the United States have been found to have a number of clinical effects in addition to their antihistaminic properties; examples are ketotifen, olopatadine, and azelastine. The derivation of these compounds is summarized in Table 33.3 (2,5,7,18). Although many of their mechanisms of action are unknown, they have been hypothesized to act on mast cells and basophils by preventing calcium influx or intracellular calcium release which interferes with activation and release of potent bioactive mediators (29). Azelastine has been demonstrated to inhibit superoxide generation by eosinophils and neutrophils which may represent one of its important anti-inflammatory mechanisms (30). These drugs can bind to H_1-receptors in a competitive and noncompetitive manner (7,31–33) In addition to their calcium-antagonistic activity, they have variable amounts of antiserotonin, anticholinergic, and antileukotriene activities (2,30,34).

Pharmacokinetic information for oral antihistamines is summarized in Table 33.2 (2,19). Cetirizine, azelastine, and ebastine may have modest antiasthma effects that are not mediated through H_1Rs. These effects include inhibition of eosinophil chemotaxis, their adherence to endothelial cells, and their recruitment into the airways after allergen challenge (7,35). Olopatadine is a compound that has been demonstrated to have strong mast cell stabilization and H_1R-antagonistic properties; it is available as an ophthalmologic solution or a nasal spray (36).

OTHER AGENTS WITH ANTIHISTAMINE PROPERTIES

Tricyclic antidepressants originally synthesized for their antihistaminic properties in the 1950s, were never fully developed as antihistamines once they were recognized to have impressive antidepressant effects (2). Because doxepin has a very high H_1-receptor affinity, it has become an acceptable alternative agent for the treatment of chronic idiopathic urticaria (37). However, caution must be exercised in the elderly, because its anticholinergic properties may be

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more pronounced, leading to blurred vision, urinary retention, and tachyarrhythmia (38).

CLINICAL USE OF ANTIHISTAMINES

The ideal H_1-receptor antagonist should provide complete and rapid relief of allergic symptoms, have a moderate duration of action, and be devoid of adverse effects. Unfortunately this type of agent does not exist (2). In general, first- and second-generation agents have fairly comparable antihistaminic effects in relieving common allergic symptoms, but all have poor decongestant capabilities (2,18). H_1 antagonists have proven useful in the treatment of allergic rhinitis, allergic conjunctivitis, urticaria, asthma, and anaphylaxis (2,7,13,16,39). The treatment of these disorders is discussed in other chapters of this book.

Numerous studies have compared the antihistaminic efficacy of second-generation antagonists with that of first-generation antagonists in the treatment of allergic rhinitis. Results have uniformly shown these agents to be more effective than placebo, but just as effective as first-generation agents, such as chlorpheniramine, using comparable dosing schedules (28,29,40,41). Studies comparing second-generation agents to one another have found no dramatic differences in their clinical effects (22,23,40).

Studies have reported that topical eye preparations of H_1-antagonists are very effective for the treatment of allergic conjunctivitis (2,7,42). While other topical antihistamine preparations are available for skin conditions, their prolonged use is not recommended owing to an elevated risk of contact sensitization (27). While many clinicians have their favorite regimens for chronic idiopathic urticaria, all of the first- and second-generation agents have been reported to be effective for patient treatment (43,44). Some types of urticaria respond better to a given antihistamine; cyproheptadine as the preferred treatment for cold-induced urticaria is an example (45). In patients with refractory chronic urticaria, combinations of nonsedating with both sedating H_1 antihistamines and H_2 antihistamines may be helpful but the level of scientific evidence supporting this combination of therapy is low (46,47).

A position paper from the American Academy of Allergy, Asthma and Immunology addressing the use of antihistamines in asthmatics has served to clarify controversy surrounding their use in patients with this disease (48). Previously it had been believed that the anticholinergic properties (i.e., dryness of the airways) of these antagonists could contribute to asthma exacerbations; it is now known that antihistamines, including some of the dual-action compounds,

may actually serve a beneficial role in the treatment of asthma because of their bronchodilator and anti-inflammatory activities (30,49). Although, these agents are not considered first-line therapy for asthma, they are certainly not contraindicated in asthma patients who require them for concomitant allergic problems (49). The *Physicians' Desk Reference* has subsequently modified warnings stating they should be used cautiously in patients with concomitant asthma (19).

Histamine is increased during the early and late airway response after specific allergen provocation and during spontaneous asthma exacerbations. Histamine can exert many of the physiologic sequelae leading to asthma including cough by direct stimulation of the sensory nerves, smooth muscle constriction, mucous hypersecretion, increased permeability of the pulmonary epithelium, vasodilation, and extravasation of fluid at the postcapillary venule level (2,7). Many studies have shown that antihistamines are bronchoprotective depending on the stimulus. For example, antihistamines attenuate bronchospasm induced by adenosine by 80%, but have little or no effect against methacholine, leukotriene, agonists, or neurokinin A (2,7,35,50).

Antihistamines serve as important adjuncts in the management of anaphylaxis, but should never replace the first-line therapy, which by general consensus is epinephrine given by intramuscular injection (13,51). Antihistamines are commonly used to treat atopic dermatitis, but are no more effective than placebo (52). Although H_1-antihistamines may be useful as an add-on therapy for eczema, there is no evidence to support their use as a monotherapy (31). The sedating first-generation antihistamines, such as diphenhydramine and hydroxyzine, are often more effective than nonsedating agents for controlling pruritus of atopic dermatitis during acute flares because they allow the patient to sleep and help break the itch–scratch cycle, but are not recommended for long-term use in children (32,33,52,53).

As with any other medication, antihistamines should be used cautiously during pregnancy (13). Long-term clinical experience using antihistamines during pregnancy has shown that tripelennamine, chlorpheniramine, and diphenhydramine cause no greater risk for birth defects than experienced by the normal population (54,55). Chlorpheniramine, diphenhydramine, loratadine, and cetirizine are all classified as pregnancy category B, indicating that no birth defects have been observed in animal models (19). However, animal studies have associated hydroxyzine with toxicity when given in high doses, and sedating antihistamines given late in the third trimester may cause adverse

effects such as tremor, paradoxical stimulation and irritability in neonates (27). If the benefits of therapy are considered to outweigh the risks, then loratadine and cetirizine are preferred in pregnancy (47). Antihistamines are excreted in breast milk and therefore infants of nursing mothers who were taking first-generation antihistamines have been reported to experience drowsiness and irritability; the antihistamines loratadine, cetirizine, and fexofenadine have not been reported to cause symptoms in babies being breastfed by mothers on these medications (56).

Antihistamines are also useful in treating nonallergic disorders, such as nausea, motion sickness, vertigo, extrapyramidal symptoms, anxiety, and insomnia (2,7). Diphenhydramine and promethazine, in particular, have antiemetic properties that are useful for treating Ménierè's disease and other vestibular disorders (27). Studies evaluating these agents in the treatment of children with otitis media and upper respiratory infections have found they offer no significant benefit when used as solo agents (57,58). However, children with recurrent otitis media and a strong family history for allergies should be evaluated by an allergist to identify potential environmental triggers and implementation of treatment with avoidance measures and a combination of antihistamines, decongestants, cromolyn, and/or topical intranasal corticosteroids, to reduce inflammation and secretions which could be contributing to recurrent infections.

The use of second-generation over first-generation antagonists as first-line agents has previously been considered premature by many experts. If a first-generation agent is taken on a regular basis at bedtime, its sedative side effects are often well tolerated by many patients. However, because some patients do not tolerate these agents, they require treatment with second-generation nonsedating agents. These agents have been well documented to consistently cause less impairment of cognitive and psychomotor skills, such as learning, reaction times, driving, memory, tracking, perception, recognition, and processing (2,7). Impairment of these functions increases indirect costs associated with the treatment of allergic rhinitis, including missed days from work or school and decreased concentration and performance while at work, resulting in overall decreased productivity (2,7). The Joint Task Force on Practice Parameters for the diagnosis and management of rhinitis has recommended that second-generation, nonsedating antihistamines be first-line treatment of perennial and seasonal allergic rhinitis to avoid potential CNS side effects (59). However, if individuals have nonallergic rhinitis with or without an allergic component manifested as severe postnasal drainage, it may be necessary to use first-generation antihistamines with or without decongestants to take

advantage of their anticholinergic drying effects. In these situations, it is best to dose the sedating antihistamine at bedtime as the sedative carry-over effect the following morning of these agents does not usually cause impaired cognitive performance. In general, it is important to educate the patient about the advantages and disadvantages of sedating and nonsedating antihistamines in the management of specific allergic diseases. The use of either or both agents should be appropriately tailored to the patient's individual needs and tolerance. Patients should be advised that the efficacy of antihistamines is greater when they are taken on a regular basis, as opposed to being taken only as needed (47).

In children, second-generation H_1-antihistamnes (cetirizine, loratadine, and fexofenadine) should be the first-line therapy for allergic rhinitis, chronic spontaneous urticaria, and urticarial reactions resulting from food allergy (60). First-generation H_1-antihistamine licensed dosages vary across countries and do not appear to be evidence based; therefore, their safety and efficacy is not assured (61).

ADVERSE EFFECTS OF H_1-ANTAGONISTS

The numerous side effects of first-generation antihistamines have been attributed to their affinity for P glycoprotein and their lipophilicity, resulting in the ability to cross the blood–brain barrier (62). In addition, they are relatively nonselective resulting in anticholinergic activity (63). The side effects of first-generation antihistamines vary in character and severity among the structural subclasses. For instance, the ethylenediamines (PBZ) have more pronounced gastrointestinal side effects, whereas the ethanolamines such as diphenhydramine have increased antimuscarinic activity and cause a greater degree of sedation in patients. This is potentially hazardous in the older population, and may also severely affect learning and safety in children, and so the dosage is modified accordingly in vulnerable populations (38,47,64). The alkylamines such as chlorpheniramine have milder CNS side effects and are generally the best tolerated among the first-generation agents (65).

Specific side effects of first-generation agents include impaired cognition, slowed reaction times, decreased alertness, confusion, dizziness, tinnitus, anorexia, nausea, vomiting, epigastric distress, diarrhea, and constipation. Associated anticholinergic side effects include dry mouth, blurred vision, and urinary retention; first-generation agents also potentiate the effects of benzodiazepines and alcohol (13,65). Caution should be exercised when treating patients at risk of glaucoma, epilepsy, hypotension, dementia, and cardiac

arrhythmias (47). Cyproheptadine, a piperidine derivative, has the effect of causing weight gain in some patients (14,16). A recent systematic review evaluating the effect of drugs with anticholinergic activity on health outcomes found that these medications have a significant adverse effect on cognitive and physical function, but there was limited evidence for their effect on delirium or mortality outcomes. This analysis further emphasizes the importance of discussing these potential side effects with patients prior to initiation especially if they are going to be used long term (66).

Intentional and accidental overdose, although uncommon, has been reported with these drugs (13). Adults usually manifest symptoms of CNS depression, whereas children may exhibit an excitatory response manifested as hyperactivity, irritability, insomnia, visual hallucinations, and seizures. Even with normal doses, it is not unusual for children to experience a paradoxic excitatory reaction. Malignant cardiac arrhythmias have been known to occur with overdoses, emphasizing the need to act expeditiously to counteract the toxic effect of these agents (13,65). Caution should be exercised using antihistamines in elderly patients or in those with liver dysfunction because of their slower clearance rates and increased susceptibility to overdose (13). Polypharmacy (comedication with five or more drugs) is a serious risk factor in the elderly, with strong anticholinergic antihistamines being a common cause of adverse drug events. Therefore, deprescribing of nonessential medication should be considered (67). Because first-generation H_1-antihistamines are secreted in breast milk, caution should be exercised using these agents in lactating women (56,65). Patients taking rupatadine should be made aware that its blood levels are increased by grapefruit juice, whereas those taking fexofenadine advised that blood levels are reduced by grapefruit and orange juice (47).

The second-generation agents have substantially fewer associated side effects. Sedation and other side effects associated with first-generation agents have been noted to occur, but generally at a rate similar to placebo (13). No longer available in the United States, terfenadine and astemizole were very occasionally associated with torsades de points. Newer second-generation antihistamines, such as fexofenadine and loratadine, have not been reported to cause cardiotoxicity (7). Cetirizine is considered a low-sedating antihistamine but is generally well tolerated by most patients, especially if dosed at bedtime. The newer second-generation antihistamines, desloratadine and levocetirizine, have thus far been demonstrated to be very safe and well tolerated. Rarer adverse effects of antihistamines include palpitation, arrhythmias, extrapyramidal symptoms, disturbed sleep, depression, convulsions, tremor, liver dysfunction,

blood disorders, angle-closure glaucoma, and hypersensitivity reactions, such as anaphylaxis, angioedema, bronchospasm, photosensitivity, and other rashes (27).

TOLERANCE

Tolerance to antihistamines is a common concern of patients taking these agents chronically. This phenomenon has been speculated to occur because of autoinduction of hepatic metabolism, resulting in an accelerated clearance rate of the antihistamine. However, studies have failed to confirm this hypothesis, and most reports of tolerance to antihistamines are now believed to be secondary to patient noncompliance because of intolerable drug side effects or breakthrough symptoms owing to severity of disease (2). Short-term studies evaluating tolerance to second-generation agents have found no change in their therapeutic efficacy after 6 to 8 weeks of regular use (2,13). Studies up to 12 weeks found no evidence that second-generation agents cause autoinduction of hepatic metabolism, leading to rapid excretion rates and drug tolerance. The clinical efficacy of these agents in the skin and treatment of allergic rhinitis does not decrease with chronic use (65). Tolerance of the sedative effects of antihistamines is more common than tachyphylaxis of their antihistaminic effects (27).

SYMPATHOMIMETICS

Many of the first-generation antihistamines, and now second-generations have been formulated in combination with decongestants. The decongestants currently used in most preparations include phenylephrine hydrochloride or pseudoephedrine hydrochloride. These agents have saturated benzene rings without 3- or 4-hydroxyl groups, which is the reason for their weak α-adrenergic effect, improved oral absorption, and duration of action. Compared with other decongestants, these agents have less effect on blood pressure and are less apt to cause CNS excitation manifested as insomnia or agitation. Phenylpropanolamine was removed from the US market because of concerns regarding hemorrhagic stroke in women taking this medication. Pseudoephedrine, the most effective of the α-adrenergic agonists, has been designated as a Schedule V over-the-counter drug product because of issues with individuals using this compound to manufacture methamphetamines; several studies have reported fewer visits to the emergency department for methamphetamine-related burn incidents caused by illicit lab fires since this law went into effect (68). Phenylephrine is a weaker α-adrenergic agonist available in many over-the-counter cough and cold formulations. Currently, questions remain regarding safety of these agents in

children; in addition, their efficacy in clinical trials at the dose available in these preparations is unclear (69).

H$_2$-ANTAGONISTS

H$_2$-histamine antagonists were first synthesized in 1969 for the purpose of developing a drug capable of inhibiting gastric acid secretion (70). These agents have a close structural resemblance to histamine, because most are simple modifications of the histamine molecule itself (71). Histamine's affinity for H$_1$-receptors is 10-fold greater than for H$_2$-receptors (71). H$_2$-antagonists are weak bases with water-soluble hydrochloride salts and tend to be less lipophilic than H$_1$-antagonists (7). Cimetidine was introduced to the United States in 1982 and has been proven safe and effective in the treatment of peptic ulcer disease (71). Cimetidine and oxmetidine resemble the earliest agents structurally, because they have an imidazole ring similar to histamine's structure. The newer agents vary structurally by having different internal ring components. For example, ranitidine has a furan ring, whereas famotidine and nizatidine are composed of thiozole rings (71). H$_2$-antagonists act primarily by competitive inhibition of the H$_2$-receptors, with the exception of famotidine, which works noncompetitively (71). The four available agents all have potent H$_2$-antagonistic properties; they vary in their pharmacokinetics and adverse effects, such as drug interactions. Several H$_2$-antagonists are now available over the counter (7,71).

Numerous studies have been undertaken to examine the clinical utility of H$_2$-antagonists in allergic and immunologic diseases. Although several studies report these agents have promising immunologic changes *in vitro*, these findings have not been substantiated clinically (7,72). Generally, H$_2$-antagonists have limited or no utility in treating allergen-induced and histamine-mediated diseases in man (72). One notable exception to this rule may be their use in combination with H$_1$-antagonists in the treatment of chronic idiopathic urticaria although the evidence supporting this combination is low (46,73). The studies evaluating the H$_2$-antagonists' clinical efficacy in allergic and immunologic disorders are extensively reviewed elsewhere (7,71).

H$_3$-RECEPTOR ANTAGONISTS

H$_3$-receptors act as presynaptic autoreceptors that inhibit synthesis and release of histamine from neurons in the CNS. Near exclusive expression in the nervous

system and an extensive variety of isoforms make H_3R distinct from the other HRs (74). H_3-receptors also exist as receptors on nonhistaminergic neurons, regulating the release of neurotransmitters such as dopamine and noradrenaline. Subsequent studies have been directed toward finding a selective H_3-antagonist. Two such agents have been synthesized: JNJ7777120 and thioperamide, a derivative of imidazolylpiperidine. They both have demonstrated H_3-receptor selectivity, but are available only for experimental use (12). There are some therapeutic agents available, such as betahistine, which act through the H_3R and may be helpful in treating vertigo, although more rigorous research is necessary (75). Evidence is growing for the role of the H_3R in cognitive function, sleep physiology, pain physiology, feeding behavior, and fear memory (76). It is of interest as a drug target for treating neurologic/neurodegenerative diseases such as Alzheimer and Parkinson diseases as well as other neuropsychiatric disorders such as drug addiction and Tourette syndrome (74).

H_4-RECEPTOR ANTAGONISTS

The H_4 receptor is primarily expressed on immunologic cells, such as eosinophils, mast cells, T cells, and dendritic cells. The H_4 receptor is approximately 35% homologous with the H_3R. Many of the known H_3 agonists and antagonists also bind the H_4R; examples include thioperamide and JNJ7777120. Ongoing clinical research suggests the efficacy of an H_4R antagonist, which may be an available therapy in the near future for asthma and the pruritus of atopic dermatitis, which have been unresponsive to antihistamines targeting the H_1R and H_2R (77). In addition, the H_4R antagonists may have a role in the eventual treatment of chronic inflammation, pain, itch, cancer, diabetes and related complications (i.e., neuropathy), gastrointestinal, endocrine, and salivary/exocrine disorders (76).

CONCLUSIONS

The discovery of H_1-receptor antagonists has proven to be a significant breakthrough in the treatment of allergic diseases. Chemical modifications of these early agents have yielded the second-generation antihistamines, which are of equal antagonistic efficacy but with fewer side effects. Newer nonsedating antihistamines, which are metabolites or isomers of existing agents, are now under development. H_2-receptor antagonists have been found extremely useful in the treatment of peptic ulcer disease. However, they have not proven to be very

useful in the treatment of allergic and immunologic disorders in humans. Owing to better side effect profiles, newer, selective nonsedating H_1-antagonists and dual-action antihistamines have provided therapeutic advantages over first-generation agents for long-term management of allergic diseases, including rhinitis, conjunctivitis, and urticaria.

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β Agonists

RACHEL G. ROBISON AND JACQUELINE A. PONGRACIC

Bronchodilators represent an important component of asthma therapy. Among the various agents available for this purpose, β-adrenergic agonists are the most commonly used. This class of medications is currently used for both relief of acute symptoms and prevention of symptoms. Short-acting β agonists (SABA) are the mainstay of rescue therapy. The availability of long-acting preparations has paved the way for β agonists to be used for disease control.

◼ HISTORIC PERSPECTIVES

Sympathomimetic agents have been used to treat asthma for thousands of years. Ephedrine, which is found in Ma huang (*Ephedra sinica*), has been used by the Chinese since 3000 BC. Because its therapeutic benefits were noted to wane over time, while adverse reactions such as central nervous system stimulation increased, new and improved sympathomimetic agents were highly desired. Subcutaneous injections of adrenaline were not only used in the early 1900s but were also associated with unacceptable side effects. It was only 70 years ago that the first β-adrenergic agonist, isoproterenol, appeared on the scene (1). As a potent, nonselective β agonist, isoproterenol was associated with many side effects but less than occurred with adrenaline. These toxicity issues and the identification of α and β-adrenoreceptors led to the development of the β_2-selective agonist, albuterol, in the 1960s. Since then, a variety of inhaled β_2-selective agonists have been developed. Pirbuterol, terbutaline, and fenoterol are other, rapidly acting SABA. Fenoterol is potent, but less β_2 selective than the others, and it is not available in the United States. In response to continued concerns about side effects, further examination and refinements in these molecules have led to the production of an enantiomeric form of albuterol, called levalbuterol. Long-acting β agonists (LABA) have also become available. Salmeterol and formoterol represent this newer class of β-adrenergic agonists. Vilanterol, an ultra-LABA with a 24-hour duration of effect, has recently

become Food and Drug Administration (FDA) approved for use in patients with asthma. A list of current, FDA–approved inhaled β agonists for asthma and their properties is presented in Table 34.1.

TABLE 34.1 CURRENT, FDA–APPROVED B-ADRENERGIC INHALED AGONISTS FOR ASTHMA

NAME	CLASS	ONSET OF ACTION (min)	PEAK EFFECT	DURATION OF ACTION (h)
Albuterol	SABA	5	1 h	3–4
Levalbuterol	SABA	5–10	76–78 min	3–4
Pirbuterol	SABA	5	0.5–1 h	5
Salmeterol	LABA	10–20	3–4 h	12
Formoterol	LABA	1–3	1–3 h	12
Vilanterol	Ultra-LABA	15	1–2 h	24

FDA, Food and Drug Administration; LABA, long-acting β agonists; SABA, short-acting β agonists.

■ MECHANISM OF ACTION AND PHARMACOLOGY

β-Adrenergic agonists exert their effects through interactions with membrane-bound receptors. Three types of β-adrenergic receptors have been characterized: β_1, β_2, and β_3. β_1 Receptors predominate in the heart, whereas β_3 receptors are found in adipose tissue. β_2 Receptors are ubiquitous; in the lung, these receptors reside in smooth muscle, submucosal glands, epithelium, and alveoli as well as in smooth muscle and endothelium of the pulmonary arterial system. Radioligand binding studies and computed tomographic imaging have shown that these receptors are present in greater concentrations in the central lung and alveoli. β_2 Receptors are also found on a variety of inflammatory cells commonly associated with asthma, including mast cells, macrophages,

neutrophils, eosinophils, and lymphocytes. β_2 Receptors are present in very high concentrations in airway smooth muscle, and less so in epithelial cells, endothelial cells, type II cells, and mast cells.

The β_2 adrenergic receptor, illustrated in Fig. 34.1, is a member of a superfamily of 7-transmembrane G-protein–coupled receptors encoded by a gene on chromosome 5 (2). Initially, a lock and key mechanism by which β agonists engaged the receptor was hypothesized. However, it appears that β_2-adrenergic receptors vacillate between inactive and active states (3), and β agonists may shift the equilibrium to favor the activated state. An agonist drug, such as albuterol, binds to the extracellular domain of the receptor and induces a conformational change so that the intracellular regions of the receptor may bind to a G protein. As a result, adenylyl cyclase is activated and causes an increase in cyclic adenosine monophosphate (cAMP). cAMP acts as a second messenger by activating protein kinase A, which causes phosphorylation with resultant relaxation of airway smooth muscle. cAMP also augments intracellular calcium ion stores, leading to relaxation of airway smooth muscle.

Review of the development of β-adrenergic agents highlights the functional differences among these medications. The early β agonists were initially modeled after adrenaline and noradrenaline. Structural modifications of these catecholamines were noted to impart functional changes in these compounds. For example, substitutions in the hydroxyl groups on the benzene ring reduce inactivation by the gastrointestinal enzyme catechol *O*-methyltransferase, as is the case for albuterol, terbutaline, metaproterenol, and fenoterol. These specific alterations increase duration of action and allow for oral administration. Modifications of the side-chain increase selectivity for the β_2 receptor, reduce inactivation by monoamine oxidase, and extend duration of action, as is seen for albuterol, terbutaline, pirbuterol, and procaterol. Salmeterol and formoterol have much larger lipophilic side chains that account for their long-lasting β_2-selective effects. Despite their structural and functional similarities, salmeterol and formoterol have different mechanisms of action at the cellular level (4). Salmeterol, which is highly lipophilic, is rapidly taken up into the cell after which it gradually diffuses out to interact with the receptor. Its side chain engages with an exosite of the receptor acting as an anchor to prevent dissociation of the agonist from the receptor, whereas the rest of the molecule engages and disengages the active site of the receptor like a hinge (2). Formoterol is moderately lipophilic and has a faster onset of action, but a decreased duration of action in comparison to salmeterol. It can directly

stimulate the β_2 receptor, and a fraction can enter the cell membrane in depot form and slowly, gradually leach out (5,6).
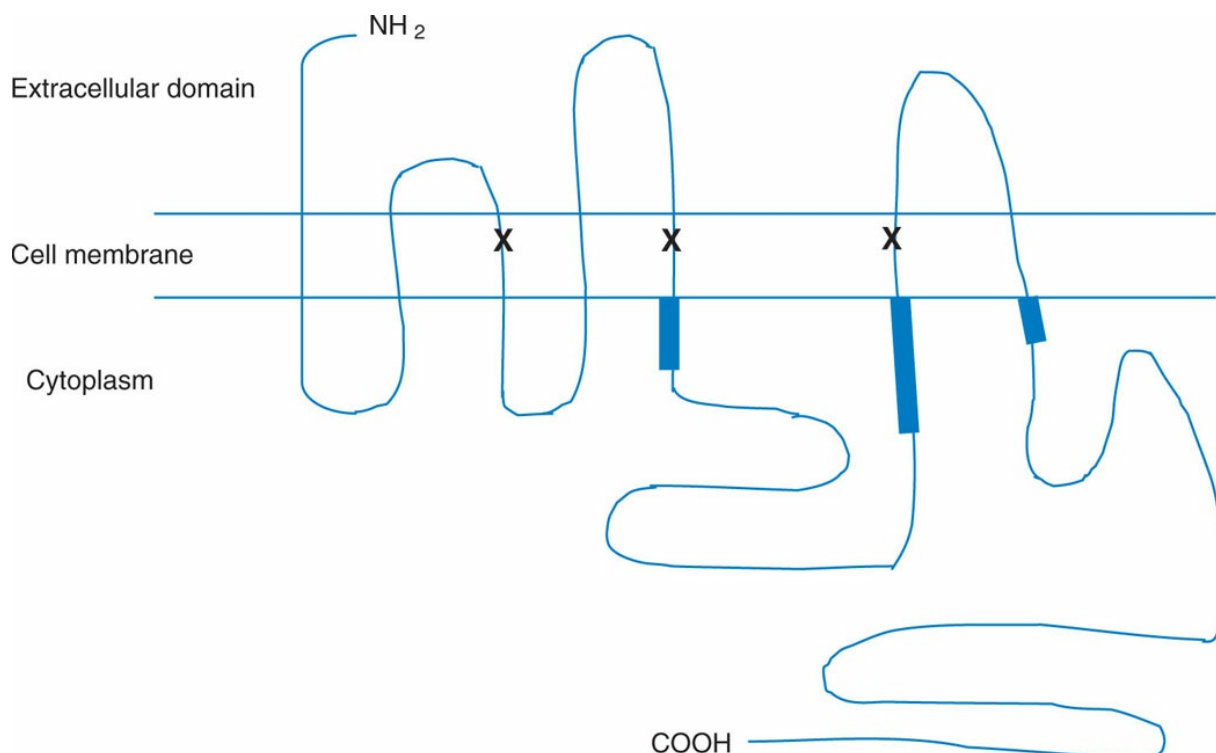
■ **FIGURE 34.1** The structure of the human β_2-adrenergic receptor. Regions involved in G-protein coupling bolded. Sites involved in β_2-agonist building are marked as X.

The response to β agonists also varies by polymorphisms of the β_2-adrenoceptor and other genetic interactions. There are two *ADRB2* genes for the receptor so that individuals may be homozygous or heterozygous for any given polymorphism. The *ADRB2* single nucleotide polymorphism most often associated with altered bronchodilator response is located at codon 16, with substitution of arginine for glycine. As a result, there are three possible genotypes: Arg/Arg, Arg/Gly, and Gly/Gly (7). The frequency of these genotypes differs among populations. For example, the Arg/Arg genotype is about half as common in white people (12% to 14%) versus black people (22% to 26%) (8–10). Studies have found that Arg/Arg homozygotes have a decreased therapeutic response or worsening pulmonary function and increased risk of exacerbations during regular use of SABA (11–13). Some, but not all, studies have shown that mutations at codons 16 and 27 are associated with altered bronchodilator responses (14,15) and pulmonary function (11,12). Such effects have not been substantiated for LABAs, because a large prospective clinical trial found no evidence of a pharmacogenetics effect of *ADRB2* on salmeterol

(LABA) response (16). More recently, *ADRB2* research has expanded to include gene regulation and associated signaling pathways. Nitrosylation pathway genes have been demonstrated to interact with *ADRB2* to alter response to albuterol therapy. For example, interactions between genetic variants of GSNOR and *ADRB2* were associated with a lack of response to albuterol in black children with asthma (17).

■ SHORT-ACTING β AGONISTS

SABAs induce relaxation of airway smooth muscle quickly. For example, albuterol produces bronchodilation within 5 minutes of inhalation. Its pharmacologic effects peak after 60 to 90 minutes and last 3 to 4 hours and sometimes as long as 6 hours. Because β_2 receptors are also found on a variety of inflammatory cells, investigators have postulated that β_2 agonists may also possess anti-inflammatory effects. Albuterol inhibits histamine release from activated mast cells *in vitro* (18). Inhibitory effects have also been demonstrated on eosinophils (19–22), lymphocytes (23,24), and neutrophils (25,26). *In vivo* studies of albuterol have failed to uphold an anti-inflammatory effect and, in fact, show a potentiated late-phase response, elevation in sputum eosinophils, and increased number of activated eosinophils in bronchial biopsy specimens (27,28).

Until 1999, all SABAs used in the United States have been racemic mixtures of two mirror-image stereoisomers, called R and S, in equal parts. (R)-isomers induce bronchodilator responses, whereas (S)-isomers do not. *In vivo* studies have demonstrated that regular use of racemic albuterol is associated with increased airway responsiveness to allergen (28,29). *In vitro*, (R)-albuterol induces bronchodilation in isolated human trachea (30), whereas (S)-albuterol augments contractile responses to histamine and leukotriene C4 in bronchial tissue (31). (S)-albuterol has much less affinity for β_2 receptors than does (R)-albuterol (32). (S)-albuterol appears to have pro-inflammatory effects as well, with evidence of eosinophil activation demonstrated through elevations in superoxide and eosinophil peroxidase (33,34).

In vivo, differences between (R)-albuterol and (S)-albuterol are also evident. (S)-albuterol is metabolized 10 times more slowly than (R)-albuterol (35–37) and is detectable in the blood stream for up to 24 hours after administration of racemic albuterol (36). Formulations of (R)-albuterol, called levalbuterol, are available for nebulized and metered-dose inhaler (MDI) administration. The safety and efficacy of levalbuterol in adults and children has been well

documented. A multicenter randomized study in 362 teenagers and adults with moderate-to-severe asthma reported that 0.63 mg of levalbuterol was as effective as 2.5 mg of racemic albuterol (38). Because of the flat dose–response curve, this study failed to show a significant difference with regard to efficacy between levalbuterol and racemic albuterol. Similarly, there was no difference in dose-dependent side effects between levalbuterol and racemic albuterol. In a smaller study of levalbuterol and racemic albuterol in children, lower doses of levalbuterol were as effective as 2.5 mg of racemic albuterol, and all treatments were equally well tolerated in terms of side effects (39).

LONG-ACTING β AGONISTS

Two LABAs are currently approved for use in people with asthma in the United States: salmeterol and formoterol. Introduced to the market in the 1990s, LABAs provide bronchodilation for 12 hours. The onset of action varies between LABAs. For instance, salmeterol effects are seen in 10 to 20 minutes, whereas formoterol actions begin in as little as 1 to 3 minutes. In addition to their bronchodilatory properties, LABAs have bronchoprotective effects and promote translocation of the glucocorticoid receptor to the nucleus to stimulate gene transcription.

Though LABAs have not been shown to exert significant anti-inflammatory effects *in vivo*, by enhancing glucocorticoid activity their use appears not to be pro-inflammatory or to enhance airway inflammation (40).

CLINICAL USE OF β AGONISTS IN ASTHMA

Current national and international guidelines promote the regular daily use of anti-inflammatory, or "controller," agents for persistent asthma (41,42). Despite the use of controller therapy, some individuals may develop breakthrough symptoms or acute exacerbations of their disease. SABAs are recommended for the relief of acute asthma symptoms and are recommended as first-line therapy to relieve bronchoconstriction during acute asthma exacerbations in the emergency department. SABAs are preferred over other bronchodilators, such as methylxanthines and anticholinergic agents, because SABAs exhibit faster onset of action without significant adverse effects when used appropriately. Asthma guidelines also suggest that the frequency with which SABAs are needed for symptom relief serves as a useful marker of asthma control and of the need for adjusting anti-inflammatory therapy. In fact, SABA prescription refills have been shown to be a good marker for asthma morbidity, with refills typically occurring on or the day after asthma-related emergency department visits and

hospitalizations (43).

SABAs may also be used to confirm the diagnosis of asthma by establishing whether reversible bronchospasm exists (41).

SABAs are also effective for the prevention of symptoms, such as exercise-induced bronchospasm, when used 5 to 15 minutes before exercise (44,45). Given their short duration of action, SABAs are not well suited for the prevention of nocturnal symptoms.

Randomized controlled trials of levalbuterol versus albuterol conducted in the emergency department have shown conflicting results for superiority of levalbuterol on hospitalization rates (46), time to discharge (47), and clinical improvement (48). Levalbuterol may be a suitable alternative for patients who experience intolerable side effects from racemic β agonists although there does not appear to be a clear consistent advantage in the literature.

The regular daily use of SABAs is generally not recommended, but this has been a source of controversy for many years. Although some reports maintain that routine use of SABAs is safe and effective, other studies have reported detrimental effects. Several studies have demonstrated a reduction in forced expiratory volume in 1 second after regular SABA use (49–54). Increases in bronchial reactivity have also been noted (49–57). Although some prospective studies of regular inhaled SABA use failed to demonstrate deterioration in asthma (58–61), other studies have shown deleterious effects in as little as 3 weeks (49). Because there has been no evidence that the regular use of SABAs improves long-term asthma control, their regular use is not advised. The National Asthma Education and Prevention Program Expert Panel Report 3 clearly states that anti-inflammatory treatment should be considered when SABAs are needed more than 2 days/week (41).

The situation appears to be quite different for LABAs. In light of their slower onset of action, LABAs are not recommended for relief of acute symptoms (62). This class should be used daily to improve asthma control. Though initially used for monotherapy or as an add-on to inhaled corticosteroids (ICSs), LABAs are now solely recommended to be used in combination with ICS in asthma. The addition of LABAs to ICS has been established to improve asthma control more so than increasing ICS dose alone in patients who have persistent asthma symptoms while taking ICS (63). This effect is independent of the ICS dose. LABAs block exercise-induced bronchoconstriction (64,65). Regular use of LABA provides protection of exercise-induced symptoms for up to 5 hours (41). This class is also better suited for control of nocturnal asthma (62,66). Based on

the benefits demonstrated in these studies, LABAs should be used in conjunction with ICSs for the management of asthma that is inadequately controlled with low-dose ICSs.

ADVERSE EFFECTS

A variety of side effects have been described with the use of β agonists. Given the widespread distribution of β_2 receptors in the body, many organ systems may be affected. The most common complaint is tremor, which is caused by stimulation of β_2 receptors in skeletal muscle. Restlessness is also commonly reported. Mediated by β vascular relaxation in skeletal muscle, cardiac stimulation occurs as a result of decreased peripheral resistance with resultant sympathetic output. Tachycardia and palpitations are much less frequent when usual doses are administered through inhalation in contrast to oral or intravenous administration. It is important to note that prolongation of QTc may lead to arrhythmias or myocardial ischemia in susceptible patients. Transient decreases in PaO_2 may occur when vascular dilation and increased cardiac output enhance perfusion to underventilated areas of lung. Abdominal complaints are sometimes seen in children receiving aggressive therapy for management of severe, acute asthma. Metabolic effects include hyperglycemia (because of glycogenolysis) and reductions in serum potassium and magnesium. Intracellular potassium shifts occur as a result of direct stimulation of the Na^+–K^+ pump. Magnesium also moves in this manner, but increased urinary excretion further contributes to the reduction in this cation. Randomized controlled trials comparing albuterol and levalbuterol have found the frequency and types of adverse events to be similar (46,48,67).

Paradoxic bronchospasm may occur after the use of β agonists. Despite the low frequency with which this occurs, such reactions may be quite severe, and even life-threatening (68). Warmth, flushing, pruritus, nasal obstruction, and laryngeal wheeze are frequently noted to accompany acute bronchospasm. Paradoxic bronchospasm is associated with use of new MDIs and bottles of nebulized solutions. Propellants have been implicated because they account for 58% to 99% of the composition of MDIs (68). For nebulized solutions, other possible factors have been suggested, such as acidity, osmolality, and preservatives, specifically benzalkonium chloride, ethylenediaminetetraacetic acid, and sulfites (69). Contamination of nebulized solutions, particularly from multidose bottles, may also contribute to this problem. The detrimental effects of (S)-albuterol may also account for paradoxic bronchospasm (70).

Short-term loss of effectiveness, or tachyphylaxis, occurs for β agonists as it commonly does with agonist–cell surface receptor interactions. This occurs in response to continuous or frequent, repetitive use. Whether clinically relevant tachyphylaxis to the bronchodilatory effect exists remains controversial. Tolerance has also been demonstrated in some, but not all, studies of long-term, inhaled β agonist use in as little as 3 weeks of repeated use, particularly affecting the duration rather than peak response (71–73). Table 34.2 summarizes problems associated with the regular use of β agonists.

β AGONISTS AND SAFETY

Two major epidemics prompted international concern and investigation into the relationships between β agonists and asthma deaths. The first epidemic occurred in the 1960s, when a 2- to 10-fold increase in asthma mortality rates was noted in six countries, including the United Kingdom and Norway. Initial evaluation did not find the rise to be related to changes in diagnosis, disease classification, or death certificate information (74). Because MDI β agonist preparations had been introduced in the early 1960s, investigators pursued the possibility of a new treatment effect. A high-dose isoproterenol forte preparation was in use only in the countries affected by the epidemics at the time. Case series analysis revealed that many of those who died of asthma used excessive amounts of this high-dose product (75). Removal of this product from the market was followed by a reduction in mortality. It was thought that the deaths had been caused by cardiac toxicity of this nonspecific β agonist. The second epidemic occurred in New Zealand 10 years later. Epidemiologic studies found that the risk for asthma death was increased in those patients who had been treated with another potent but less β_2-selective agent, fenoterol (76). Case–control studies found that it had been prescribed more often to those who died, but some investigators believed that these findings may have been confounded by asthma severity. After removing the product from the market, mortality declined. Theories for the mechanisms by which β agonists cause harm include adverse cardiac effects, tachyphylaxis, and masking of exacerbation severity.

TABLE 34.2 UNTOWARD EFFECTS ASSOCIATED WITH THE REGULAR USE OF β AGONISTS

PROBLEM	SABA	LABA
Tolerance (↓ bronchodilator response)	Y	Y

↓ FEV$_1$	Y	N
↑ Response to bronchial challenge	Y	Y
Loss of bronchoprotection	Y	Y
↓ Protection against EIB	Y	Y
Cardiac toxicity	Y	N
↓ Response to SABA	Y	Conflicting results

EIB, exercise-induced bronchoconstriction; FEV$_1$, forced expiratory volume in 1 second; LABA, long-acting β agonists; SABA, short-acting β agonists.

Studies have tried to assess similar risks for LABA. The Serevent Nationwide Surveillance study enrolled more than 25,000 adults in a randomized, double-blind study comparing salmeterol and salbutamol in parallel, but had insufficient power to establish relative risk because of the low number of deaths from asthma (12 deaths in salmeterol subjects versus 2 in salbutamol subjects) (77). The Salmeterol Multicenter Asthma Research Trial showed a small increase in respiratory and asthma-related deaths in adolescents and adults with unstable asthma in the salmeterol group when compared to a placebo group. The study was prematurely ended in 2003 after interim analysis detected this increase which was statically significant in African Americans. Notably, only 47% of the study population used a baseline ICS (49% in Caucasians and 38% in African Americans) (78).

In response to these concerns, the FDA placed a black-box warning on all LABA medications in 2006. Subsequent changes following FDA advisory committee meetings in 2010 led to the recommendation that LABAs, even in combination with ICS, only be used for short periods to achieve control and then whenever possible the therapy be stepped back down to ICS alone (79). Because death is a rare occurrence in asthma clinical trials, systematic meta-analysis type reviews based on the performed randomized controlled trials and observational studies have been utilized to better understand the risk of LABA use. Evidence from these studies, although still limited by low statistical power, indicates that

the combination therapy with ICS-LABA is associated with a decreased risk of serious asthma-related events though admittedly these studies cannot definitely rule out an increased risk of fatal adverse events with addition of LABA to ICS (80).

In 2011, the FDA made a further call for LABA manufacturers to undertake randomized, double-blind, controlled clinical trials comparing the addition of LABAs to ICS versus ICS alone in at least 46,000 adolescents and adults. These studies would evaluate the combination ICS-LABAs of budesonide and formoterol, fluticasone and salmeterol, mometasone and formoterol, as well as formoterol along with fluticasone in separate inhaler devices. In addition to answering the question of ICS-LABA versus ICS alone, the results of these separate studies may also be compared to allow for determination of whether all LABAs confer a similar risk. The first of these studies performed by GlaxoSmithKline was published in the *New England Journal of Medicine* in 2016. Over 11,000 adult subjects from 33 countries were randomized to fluticasone and salmeterol diskus versus fluticasone propionate alone for the 26-week study (81). No asthma-related deaths occurred in either study arm. A total of 67 subjects had serious asthma-related events across the study. These events were evenly distributed across the two groups: 34 patients with events on fluticasone-salmeterol treatment and 33 patients with events on fluticasone-alone treatment. The risk of severe asthma exacerbation was actually 21% lower in the fluticasone-salmeterol group than in the fluticasone-only group. A pediatric trial using the fluticasone and salmeterol diskus was also performed by GlaxoSmithKline in 6,000 children aged 4 to 11 years. The children were randomized to a fixed-dose combination of fluticasone-salmeterol versus fluticasone-alone and were observed for the 26-week trial period (82). No asthma-related deaths or intubations occurred in either group. Serious asthma-related events occurred at similar numbers in both groups (27 in the fluticasone-salmeterol group versus 21 in the fluticasone-alone), thus extending the findings of the adolescent-adult trial to the pediatric age group. Results of the three other FDA–requested studies are expected in 2017.

Because the FDA recommendation is to use ICS-LABA combinations for the shortest duration possible and to step down to ICS alone once asthma symptom control is achieved, limited studies have attempted to address whether stopping ICS-LABA combinations is associated with worsening of asthma control or with an increase or a decrease in adverse events in patients with asthma. A Cochrane review, including data from five adult studies, found some reduction in asthma control scores and quality of life measurements after patients were stepped off

ICS-LABA; however, there were too few events to definitively establish whether this increased serious adverse events (83). A similar review of pediatric studies found no randomized trials suitable for inclusion in which ICS-LABA was stopped after attaining asthma control (84). Results of the Long-acting Beta Agonist Step Down Study, a blinded, double-masked parallel group study comparing the effectiveness of therapy step-down strategies in well-controlled asthmatics sponsored by the American Lung Association and GlaxoSmithKline, are anticipated to bridge this knowledge gap for asthmatics 12 years and older.

SINGLE INHALER THERAPY

Although not currently approved by the US FDA, the use of a combination inhaler containing ICS with either formoterol or albuterol has been reported in many studies for both maintenance and reliever therapy (85–87). Often referred to as single inhaler therapy (SiT) and well accepted in other countries, the strategy is part of the Global Initiative for Asthma guidelines. Budesonide-formoterol is the best studied combination medication for SiT and leverages formoterol's fast onset of action. Utilization of SiT permits patients and physicians to increase the dose of both medications simultaneously, allows for flexibility with dosing when symptoms worsen, and may allow for improved adherence for inhaler use. A Cochrane review of four studies, including more than 9,000 adults (88) using SiT, showed reductions in exacerbations requiring hospitalization, emergency room visit, and systemic corticosteroids when compared to fixed-dose controller therapy and SABAs as needed for rescue. However, there was insufficient information to determine whether the use of SiT increased or decreased adverse effects, though it is important to note that SiT did not appear to increase the overall quantity of ICS use. There are no published studies in the United States of children under the age of 12 using FDA–approved ICS-LABA for SiT.

SUMMARY

β Agonists are widely used in asthma management. Refinements in their chemical structure have led to improvements in efficacy, safety, and tolerance. Short-acting agents are indicated for the treatment of mild, intermittent asthma and for initial management of acute asthma symptoms in patients with persistent asthma. This class is also effective for the prevention of exercise-induced bronchospasm, but regular daily use of SABAs is not recommended. LABAs have a prolonged duration of action. Consequently, these agents are best used for asthma control, for example, prevention of symptoms. LABAs should not be

used as monotherapy for asthma, and current guidelines emphasize their position as adjunctive therapy in combination with ICSs. Recently published trials of the regular use of LABA in conjunction with ICSs provide reassurance with regard to safety and serious adverse events. Growing international evidence suggests that SiT containing a SABA and ICS offers advantages in terms of adherence, dose flexibility, and prevention of exacerbations. While SiT is not currently available for use in the United States, a once-daily combination ICS and ultra-LABA has recently received FDA approval. The growing evidence for efficacy and safety of ICS-LABA formulations to achieve and maintain control has transformed how β agonists are used in asthma.

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Corticosteroids in Treatment of Allergic Diseases

SNEHAL PATEL AND TARA F. CARR

HISTORY OF CORTICOSTEROID

Corticosteroids—the synthetic analogs of the glucocorticoid (GC) hormones of the adrenal cortex—have emerged as the single most effective class of drugs for treatment of inflammatory diseases. Although it was as early as 1885 that Addison (1) described a "wasting disease" after destruction of the adrenal gland, it wasn't until the 20th century that researchers defined the activity of the adrenal steroids. In 1949, Hench et al. (2,3) introduced corticosteroid treatment for arthritis and other diseases, which soon expanded to the use of corticosteroids as treatments for nearly all inflammatory diseases. Enthusiasm for systemic corticosteroid therapy waned with the discovery that chronic use caused numerous debilitating adverse effects, but the 1957 introduction of topically active corticosteroids with greatly diminished side effects renewed interest in their widespread use. Today, systemic or topical corticosteroid preparations are utilized by physicians for treatment of nearly every allergic inflammatory disease, including asthma, rhinitis, and dermatitis. This chapter reviews the physiology and pharmacology of corticosteroids and discusses the use of these important medications for treatment of allergic diseases.

PHYSIOLOGY AND PHARMACOLOGY OF CORTICOSTEROIDS

There are two general classes of corticosteroids produced by the adrenal cortex: mineralocorticoids (MCs) and GCs (also called glucocorticosteroids). GCs are essential for life and support various body functions, including fetal development, stress responses, gluconeogenesis, arousal, and immune regulation. MCs principally affect the regulation of fluid and electrolyte balance and have no clinical use in the treatment of allergic disease. However, because MC activity in corticosteroid medications may produce fluid and electrolyte side effects, they are not entirely without relevance.

The basic chemical structure of GCs consists of 21 carbon atoms with a total of four rings: three six-carbon rings and a five-carbon ring (Fig. 35.1). Hydrocortisone (the synthetic compound structurally identical to endogenous cortisol) is the parent molecule from which other natural and synthetic GCs derive. The essential features of the anti-inflammatory GC consist of the following: (a) a two-carbon chain at the 17th position, (b) methyl groups at carbons 10 and 13, (c) a ketone oxygen at C3, (d) a double bond between C-4 and C-5, (e) a ketone oxygen at C-20, and (f) a hydroxyl group at C-11. Steroid compounds containing a ketone oxygen at C-10 require reduction to a hydroxyl group for biologic activity, as in the case of prednisone conversion to prednisolone, or cortisone to cortisol/hydrocortisone. Modifications of either the nucleus or the side chains produce different GC agents with varying anti-inflammatory and MC activity as compared to cortisol. For example, addition of a 1,2 double bond, such as in the case of prednisolone, prednisone, and methylprednisone, increases the GC activity. Further alterations at the C-17 and C-21 positions result in corticosteroids with enhanced binding affinity to the glucocorticoid receptor (GR) and reduced systemic effects and thus are commonly seen in topical GC preparations. Pharmacologic variables and relative potencies for commonly used systemic GCs are presented in Table 35.1.
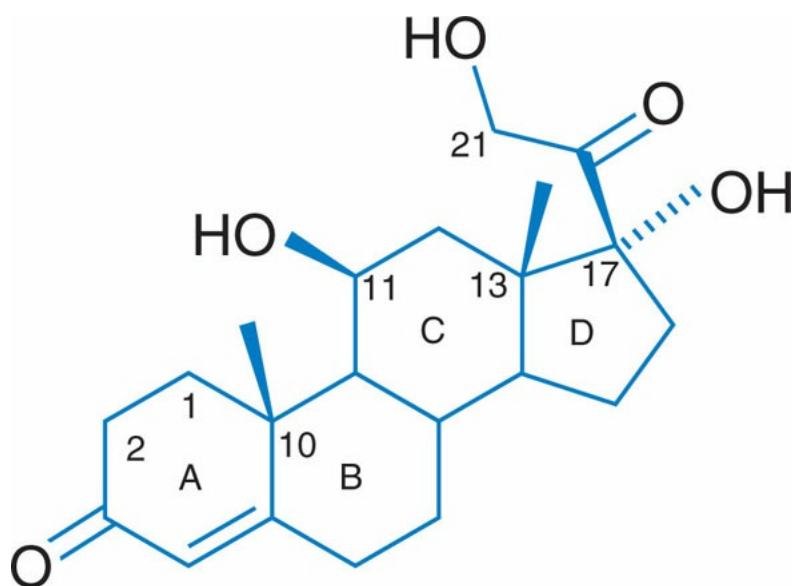
■ **FIGURE 35.1** Chemical structure of cortisol (hydrocortisone).

Cortisol secretion results from a cascade of stimulatory events in the hypothalamic–pituitary–adrenal (HPA) axis. The process begins in the hypothalamus with the secretion of corticotropin-releasing hormone, which stimulates the release of adrenocorticotropic hormone (ACTH), a product of the β cells of the anterior pituitary gland. In turn, ACTH stimulates the production of

GCs, which are primarily produced in the zona fasciculata of the adrenal cortex. Cortisol subsequently inhibits ACTH and corticotrophin-releasing factor (CRF) in a negative feedback loop.

Circulating cortisol levels follow a diurnal pattern, under control of the circadian clock. Cortisol and ACTH secretion normally reaches peak levels in the early morning around 8 AM, then declines throughout the day to a nadir around midnight (4). Timing of exogenous GC dosing to mimic physiologic cortisol release may reduce side effects and improve anti-inflammatory activity (5). Daily endogenous secretion of cortisol is about 10 to 20 mg (28 to 55 μmol), but environmental stress or increased circulating levels of cytokines, such as the pro-inflammatory interleukins (IL)-1, IL-2, IL-6, and tumor necrosis factor-α, can raise levels to as high as 400 to 500 mg (6).

Normally, 90% to 95% of circulating cortisol is protein bound; however, it is the unbound fraction that is biologically active. GCs bind principally to cortisol-binding globulin (CBG), also known as transcortin. CBG has a binding capacity of only 0.7 μmol (250 μg) cortisol per liter serum. GCs may also bind to serum albumin, which has a much lower binding affinity but high capacity. At low concentrations, approximately 90% of cortisol is plasma protein bound, and at higher concentrations of cortisol, CBG binding becomes saturated.

Because pharmacologic actions, metabolism, and excretion of corticosteroids all relate to unbound steroid concentrations, the binding of circulating steroids to CBG and albumin plays important roles in modifying GC potency, half-life, and duration of effects (7). Some synthetic GCs, such as dexamethasone, exhibit little or no binding to CBG. Further, protein binding of some GCs, including prednisolone and hydrocortisone, can exhibit nonlinear dose relationships, causing significant free GC excess at higher doses and may contribute to dosing inconsistencies (8,9). Neutrophil elastase can cleave CBG, preventing steroid binding and allowing steroid bioactivity (10).

Interconversion of active and inactive forms of GC can contribute to the regulation of GC activity at the tissue level. Cortisol is partially converted to the inactive cortisone by subtype 2 of the enzyme 11-β-dehydrogenase. This enzyme is present throughout the body and thus can reduce the local activity of cortisol (11). Subtype 1 of 11-β-dehydrogenase can, conversely, convert cortisone into the biologically active cortisol in the tissues of the renal cortex, colon, salivary gland, and placenta.

TABLE 35.1 PHARMACOLOGIC VARIABLES AND EQUIVALENT DOSES OF COMMON SYSTEMICALLY ADMINISTERED

GLUCOCORTICOIDS

SYSTEMIC GLUCOCORTICOID	POTENCY RELATIVE TO CORTISOL	RELATIVE MINERALOCORTICOID ACTIVITY	EQUIVALENT DOSE (mg)	DURATION OF ACTION (h)	PLA: HAL LIFE
Hydrocortisone	1	1	20	8–12	2
Prednisone	4	0.8	5	12–36	3.3
Prednisolone	4	0.8	5	12–36	3.3
Methylprednisolone	5	0.5	4	12–36	2.4
Triamcinolone	5	0	4	12–36	2
Dexamethasone	25	0	0.75	36–72	4
Betamethasone	25	0	0.75	36–72	6.5

The pharmacokinetic properties and resultant clinical efficacy of synthetic GCs are further determined by their absorption/oral bioavailability, volume of distribution, and clearance. Natural and synthetic steroids are lipophilic compounds readily absorbed after intravenous (IV), oral, subcutaneous, or topical administration. In general, the systemic availability of oral and IV GC preparations is high and is limited by efficient first-pass liver metabolism rather than by incomplete absorption. Diseases that affect hepatic function, as well as drugs that interfere with the liver mixed-function oxidase enzymes responsible for GC metabolism, can significantly impact the biologic availability of GCs.

Synthetic GCs developed for inhalational or topical therapy have been modified for increased lipophilicity and higher receptor affinity (12–14). These modifications improve tissue retention, duration of action, and clinical efficacy. With lower doses and less significant systemic bioavailability, patients ultimately suffer fewer systemic side effects from ongoing use of these drugs. The measurement of volume of distribution of each drug reflects the amount of

absorption from the lungs to the systemic circulation, and can be affected by water solubility of each compound (Table 35.2). The amount of drug circulating in plasma is affected by metabolism, absorption from tissue, and plasma protein-binding affinity. The summation of these characteristics for each drug ultimately affects the amount of unbound drug that will contribute to systemic side effects. Enzymatic coupling with a sulfate or with glucuronic acid forms water-soluble compounds, which leads to renal excretion. There is variable excretion via the biliary and fecal routes.

Importantly, bioavailability of the orally deposited, gastrointestinally absorbed drug for each modified compound can significantly impact pharmacologic utility and safety and is significantly impacted by delivery device/method. A portion of a dose of inhaled or intranasal GC is swallowed—estimated up to 90% with some devices—and subsequently absorbed from the gastrointestinal (GI) tract. The rest reaches the upper or lower airways and exerts the desired effect. The use of spacer devices and mouth rinsing can substantially decrease the amount of systemic exposure. Particle size of inhaler may also impact the ratio of oral and lung deposition. For the portion of drug that reaches the GI tract, the degree of hepatic first-pass metabolism differs among the GCs (Table 35.2). These properties may affect the likelihood or degree of systemic side effects seen with clinical use. Oral bioavailability is also limited by requiring local tissue activation of the prodrug, for example, conversion of ciclesonide (CIC) by pulmonary esterases to an active GC metabolite called ciclesonide-active principle (15). The therapeutic index of a drug is a measure of the separation between local efficacy and systemic exposure. In the case of inhaled GCs, fluticasone furoate (FF), mometasone furoate (MF), fluticasone propionate (FP), and CIC have the most favorable therapeutic indices, compared with beclomethasone dipropionate (BDP), budesonide (BUD), and triamcinolone acetonide (TA) (16).

TABLE 35.2 PHARMACOLOGIC PROPERTIES OF INHALED GLUCOCORTICOIDS

INHALED GLUCOCORTICOID	ORAL BIOAVAILABILITY (%)	TISSUE ACTIVATION	VOLUME OF DISTRIBUTION (L/kg)	PLASMA CLEARANCE (L/min)	HALF-LIFE
BDP/BMP	26	Somewhat (BDP to BMP)	>5.7	3.8	>5

BUD	6–11	No	2.7–4.3	1.4	<2
CIC	1	Yes	>13	2.5–3.8	<2
FLN	7	No	1.8	1.0	<2
FF	1	No	~9	0.8–1.1	>5
FP	1	No	3.7–8.9	0.9–1.1	>5
MF	1	No	4.5	4.5	>5

[a]The plasma half-life of a drug does not necessarily correspond to the duration of action of its biologic effect.

BDP, beclomethasone dipropionate; BUD, budesonide; CIC, ciclesonide; FF, fluticasone furoate; FLN, flunisolide; FP, fluticasone propionate; MF, mometasone furoate.

In summary, the ratio of desirable and undesirable effects of topical steroid preparations depends on a combination of pharmacologic properties:

- Oropharyngeal versus lower airway deposition
- Topical potency of drug in the airways (GC receptor-binding affinity)
- Systemic activity of drug after absorption by the lungs (volume of distribution) or GI tract (oral bioavailability)
- Circulating free GC (affected by clearance and protein binding)
- Activation or conversion of a GC to an active metabolite or compound

MOLECULAR AND ANTI-INFLAMMATORY MECHANISMS OF GLUCOCORTICOID ACTION

As anti-inflammatory agents, GCs exert both direct and indirect inhibitory effects on multiple inflammatory genes (encoding cytokines, chemokines, adhesion molecules, inflammatory enzymes, receptors, and proteins) that have been activated during the inflammatory process (17). The relative potency of

GCs is dependent on plasma protein-binding, intracellular receptor affinity, and receptor dissociation from activated receptors.

Unbound GC molecules diffuse readily across cell membranes and bind to GRs in the cytoplasm. The GR is a 94-kD protein which exists in the cytoplasm as a multiprotein complex containing several heat shock proteins (Hsp90, Hsp70, Hsp56, and Hsp40) (18). These heat shock proteins protect the receptor and prevent its nuclear localization by covering the sites on the receptor that are needed for transport across the nuclear membrane into the nucleus (19). GRs are widely expressed in tissue and inflammatory cells (20), undergo posttranslational modification (21), and exist in multiple isoforms which have distinct activities (22). Once corticosteroids have bound to GRs, changes in the receptor structure result in rapid transport of the GR–corticosteroid complex through the nuclear pore complex (21) into the nucleus.

Genes may be directly activated or indirectly regulated through an interaction with other transcription factors and co-activators. The number of genes regulated by GRs in any given cell is unknown, but studies place the number of steroid-responsive genes per cell at 10 to 100 (23). Once in the nucleus, in a process known as transactivation, the GR may bind as a homodimer directly to specific DNA-binding sites, that is, glucocorticoid responsive elements (GREs), to induce the production of targeted genes. During this process, binding of the GR to the GRE is mediated by elongated structures called zinc fingers. GR binding to GRE induces ribonucleic acid (RNA) polymerase activity and the subsequent expression of target genes, such as anti-inflammatory IL-10. Alterations in the genetic or base pair sequences of either the GR or GRE may interfere with binding and normal transactivation processes (24,25).

Steroids can repress gene expression through direct and indirect pathways. In a process known as *cis*-repression, the GR homodimer interacts with the so-called negative GREs to directly suppress gene expression. Through *cis*-repression, we see downregulation of genes associated with side effects of GC, including pro-opiomelanocortin, CRF-1, osteocalcin, and keratin (17). Alternatively, in a process called transrepression (26), the GR may bind to pro-inflammatory transcription factors, such as NF-κB, AP-1, NFAT, T-bet, GATA3, and STAT proteins, to name a few. Upon binding, the ability of that transcription factor to bind to its target gene promotor regions is inhibited, and specific messenger RNA (mRNA) production is downregulated. Thus, transrepression indirectly suppresses expression of inflammatory genes encoding interleukins, cytokines, and adhesion molecules (27,28). GCs can also induce

enzymes such as ribonucleases and mRNA-destabilizing proteins to suppress mRNA and prevent protein translation (29).

Apparent resistance to the effect of GCs can be germline encoded, such as in the case of familial GC resistance or changes in the GR or GRE gene sequences discussed earlier. Importantly, epigenetic effects such as posttranslational modification and histone acetylation patterns may also contribute to differences in steroid efficacy or resistance among tissues or individuals (30). Whereas acetylation of histones by the enzyme histone acetyltransferase leads to unwinding and increased transcriptional activity, histone deacetylases can reverse this process. Further, histone deacetylation of the GC–GR complex may be required for transrepression of NF-κB (31). Activity of histone deacetylases can be impaired in some chronic inflammatory diseases, such as asthma and especially chronic obstructive pulmonary disease, and can be induced by GCs, contributing to the heterogeneity of drug effect seen with the use of GCs.

GCs suppress arachidonic acid metabolism through impacting processes essential to the production of prostaglandins, leukotrienes, and other products. GCs can suppress the activity of phospholipase A_2 through the induction of annexin-1, can repress transcription of the cyclooxygenase-2 enzyme, and can induce mitogen-activated protein kinase phosphatase-1 (32).

The cellular effects of GC therapy are broadly reaching, particularly on inflammatory cells. Within 4 to 6 hours of systemic GC administration, marked decreases in numbers of circulating eosinophils, basophils, and monocytes can be measured. GCs can induce eosinophil apoptosis through caspase-3 activation, can reduce production of the eosinophil-stimulating cytokine IL-5, and can inhibit release of eosinophils from the bone marrow (33,34). Through similar mechanisms, GCs also induce apoptosis of basophils (35). Interestingly, GCs can inhibit immunoglobin E (IgE)-dependent basophil degranulation and release of histamine and leukotrienes (36,37). In contrast, circulating numbers of neutrophils increase with GCs because of neutrophil demargination, prolonged survival, and increased bone marrow production (38).

Lymphocyte subsets are variably affected by GC treatment. Total circulating lymphocyte counts generally decrease, but to a lesser extent than eosinophils and basophils. GCs impair both proliferation and cytokine expression of type 1 helper T lymphocytes and cytotoxic activities of cytotoxic T lymphocytes. Type 2 helper cells, as a significant source of the type 2 cytokines which potentiate allergic disease, are an important target of GCs for therapeutic use in allergic inflammation. GCs markedly inhibit proliferation and survival of type 2 helper

cells and block their proallergic cytokine expression. Importantly, GCs enhance the expression of IL-10 and through expression of transcription factor FoxP3, can induce the development of regulatory T lymphocytes (39). B-lymphocyte numbers are not significantly impaired by GCs. Innate lymphoid cells, particularly the type 2 cytokine producing subset, seem to be minimally impacted by GC therapy (40).

The effects of GCs on mast cells are less clear (41). Mast cell degranulation is not fully inhibited by GCs, as evidenced by sustained skin-prick test reactivity in atopic individuals using. However, some data suggest GCs can diminish mast cell activity and cytokine production of type 2 cytokines, such as IL-4, IL-5, and IL-33 (30,42). GCs can also reduce expression of chemokines important for mast cell tissue recruitment, and may impact mast cell location within a tissue (43).

Airway epithelial cells are increasingly recognized for their active role in the development and potentiation of asthma and other atopic diseases (44). GCs significantly impact epithelial function through inhibiting epithelial pro-inflammatory cytokine production and subsequent downstream leukocyte recruitment. This serves to regulate trafficking of leukocytes through inhibition of endothelial presentation of integrins, such as vascular cell adhesion protein 1 (45). GCs can also suppress secretion of mucus that leads to morbidity during asthma exacerbations.

GCs can also inhibit function of antigen presenting cells through inhibition of costimulatory molecules, and GCs have been shown to affect vascular permeability possibly through impacting inflammatory mediator production or inhibiting microvascular leak (45). GCs may reduce the proliferation and pro-inflammatory capacity of smooth muscle cells in airways that is characteristic of airway remodeling in asthma, but cannot reverse this process (46).

GENERAL PRINCIPLES OF CORTICOSTEROID THERAPY

Despite the remarkable clinical benefit of GCs for the treatment of allergic and inflammatory disease, the use of GCs at high doses and/or for prolonged periods of time can result in significant adverse effects to the patient. As discussed previously, complications of GC therapy relate to the pharmacology of the agent, dose, dosing interval, and duration of use. Local administration—topical cutaneous or inhaled nasal/bronchial—is recommended where possible to avoid or reduce systemic side effects. Regardless of the route of administration, however, a general rule of thumb with GC therapy is that clinicians should use

the lowest possible effective dose for the shortest time, and patients should undergo frequent reevaluation with the goal of eliminating GCs or reducing dosages. The following eight broad principles apply:

1. If possible, treatment agents should have little or no MC activity.

2. Patients with non–life-threatening disorders, for example, atopic dermatitis (AD) or nasal polyposis, should undergo long-term systemic GC therapy only when alternative and more conservative therapy has failed.

3. To facilitate reductions in dose and prevent use of prolonged courses of systemic GC therapy, patients should receive concurrent maximal doses of topical preparations and where possible, other classes of disease-specific steroid-sparing therapy.

4. Single-dose oral GCs should be given in the morning to minimize disruption of the HPA axis.

5. Acute allergic disease exacerbations can usually be safely treated with 3- to 10-day courses of moderate-dose daily systemic GC therapy without significant adverse effects.

6. For alternate-day systemic GC therapy, the best choices are oral agents with tissue half-lives in the 12- to 36-hour (intermediate) range, such as prednisone, prednisolone, and methylprednisone.

7. Children receiving GC therapy should be regularly evaluated for growth, especially those using both intranasal and inhaled GC therapy.

8. All patients on GC treatment should undergo frequent reevaluation to attempt to reduce the dosage or eliminate steroids altogether.

Adverse Effects of Glucocorticoid Therapy

There are many potential adverse side effects associated with prolonged and/or high-dose GC therapy. Duration of therapy, dosing regimen, and mode of administration (systemic and topical) determine the occurrence and severity of adverse effects. Side effects can affect most organ systems to a variable severity and frequency (Table 35.3). Close monitoring for side effects may include directed testing for suppression of the HPA axis, cataracts, hyperglycemia, hypertension, and osteoporosis.

Osteoporosis is one of the most common side effects in patients on long-term GC therapy, and GC therapy is the most common iatrogenic cause of osteoporosis (47). The mechanisms underlying GC-induced osteoporosis are

well described in literature. GCs decrease GI calcium reabsorption and increase urinary calcium excretion, inducing parathyroid hormone activity. GCs reduce bone formation and strength through direct reduction of osteoblasts and osteocytes. GCs also suppress growth hormone, insulin-like growth factor-1, transforming growth factor β, sex hormones, and muscle mass, further indirectly inhibiting osteoblast activity and contributing to bone loss. GCs also prolong osteoclast life span with subsequent increased bone reabsorption. Cancellous bone is most significantly affected by these mechanisms; fractures are, therefore, more common in the vertebral bodies and ribs. Bone loss occurs in two phases, with pronounced bone loss of approximately 12% during the first few months of GC treatment, followed by a more steady loss of approximately 2% to 5% annually. Fracture risk is associated with dose and duration of GC, low body mass index, older age of patient, and female sex.

TABLE 35.3 POTENTIAL SIDE EFFECTS OF GLUCOCORTICOID THERAPY, BY ORGAN SYSTEM

CUTANEOUS

Skin atrophy

Striae development

Delayed wound healing

Acne/folliculitis

Perioral dermatitis

Petechiae

Hypopigmentation

ENDOCRINE

Hypothalamic–pituitary axis suppression

Weight gain

Elevated blood glucose

Cushing syndrome

Hypogonadism

Dyslipidemia

Growth suppression/retardation

CARDIOVASCULAR

Hypertension (sodium retention)

Thrombosis

PSYCHIATRIC/NEUROLOGIC

Depression

Stimulation

Insomnia

Psychosis

OPHTHALMOLOGIC

Cataracts

Glaucoma

RESPIRATORY

Oropharyngeal candidiasis

Vocal cord myopathy/dysphonia

Throat irritation

HEMATOLOGIC

Thrombosis

Immunosuppression

MUSCULOSKELETAL

Osteoporosis

Muscle atrophy/wasting

Avascular necrosis[a]

Prevention, monitoring, and treatment of GC-induced osteoporosis is clearly important. Evidence indicates that long-term inhaled corticosteroids (ICS) use affects bone mineral density and risks of fractures in a dose-dependent manner that appears significant at high doses. However, GC-induced osteoporosis has been recognized even at low chronic systemic GC doses in the range of 2.5 to 10 mg prednisone daily or equivalent. This variability likely reflects the additional risk factors of each individual for osteoporosis. The duration and dose of GC should be minimized as much as possible. Guidelines from the American College of Rheumatology and National Osteoporosis Foundation (48,49) provide recommendations for prevention of GC-induced osteoporosis for patients using GC (prednisone equivalent 5 to 7.5 mg/day or higher) for more than 3 months. These include:

- Modify additional risk factors for osteoporosis.

- Initiate calcium (1,200 to 1,500 mg/day) and vitamin D (800 to 2,000 IU/day); in children, dietary intake of calcium and vitamin D should be monitored for sufficiency.

- Measure bone mineral density at the lumber spine and hip at initiation of GC therapy.

- Repeat bone mineral density testing every year as long as patient is on high-dose GC therapy.

- Initiate bisphosphonates (using caution in women of childbearing age) or teriperatide, particularly when bone mineral density testing shows reduced *T*-score. Risks and benefits of these medications should be discussed with patients prior to initiation of therapy.

- Check sex hormone levels and replace if needed.

Administration of exogenous GC can suppress function of the HPA axis and lead to disorders such as Cushing syndrome, adrenal insufficiency, and growth inhibition. The degree of suppression is largely variable patient to patient and

again, dependent on dose and duration of GC and time of day of administration. Adrenal suppression is noted to start soon after initiating GC and should be monitored in all patients receiving high-dose GC. HPA suppression is suspected in individuals with Cushingoid appearance, and in those receiving systemic GC doses of >20 mg prednisone equivalent per day, or nighttime doses of >5 mg prednisone equivalent, for more than 3 weeks. Discontinuation of GCs in these patients requires dose reduction and monitoring for withdrawal symptoms. Acute adrenal insufficiency, as in the case of acute disruption of chronic GC dosing, is a medical emergency and should be treated promptly with IV hydrocortisone (2 mg/kg initially followed by 1.5 mg/kg every 6 hours until stable and oral therapy can be initiated). All patients on chronic GC treatment should receive stress dose steroids (1 to 2 mg/kg) prior to surgery and times of acute stress, that is, infection. Stress dose steroids should be continued until the patient is stabilized, and can then be reduced or tapered back to the home oral dose.

For most patients treated with intermittent bursts of systemic steroids, as in the case of acute exacerbations of inflammatory disease, a tapering dose is not necessary if the burst is 14 days duration or less and if there is low likelihood for HPA suppression. Alternate-day dosing and tapering may be successfully utilized for many inflammatory diseases and is associated with reduced risk of side effects. For continuous treatment beyond 14 days, tapering is utilized to prevent symptoms of adrenal insufficiency and GC withdrawal. The duration of the taper and intervals for dose reduction are generally at the discretion of the provider, and numerous tapering regimens have been reported. However, patients receiving long-term GC treatment may require very slow tapering. Intermediate- or short-acting GCs are recommended to mimic endogenous cortisol production. Hydrocortisone can be used in doses divided three times daily, with decreasing doses throughout the day. Patients undergoing a steroid taper should be monitored for recurrence of inflammatory disease symptoms, as well as those of GC withdrawal, which include weakness, malaise, anorexia, GI upset, hypotension, electrolyte abnormalities, arthralgia/myalgia, and memory impairment. Symptoms of GC withdrawal syndrome can take as long as 12 months to resolve after cessation of long-term GC therapy.

Growth failure and delayed puberty are commonly experienced by children on systemic high-dose GC; however, studies have shown that children on ICS and even on intranasal corticosteroids (INS) therapy can also show growth retardation and a decreased final height. In a recent Cochrane meta-analysis, regular use of low- or medium-dose ICS for 12 months in children with mild-to-moderate asthma resulted in a mean reduction of 0.48 cm/year in linear growth

velocity and a 0.61-cm change from baseline in height. This effect is most pronounced in the first year of use compared to subsequent years (50). The most significant contributor to this growth effect is likely difference among the GC preparations themselves, rather than dose at this range, or regularity of use or device. For example, studies of CIC and flunisolide (FL) in children showed no effect on growth. Evidence of the effect of intranasal GC preparations on growth shows variable effect on growth, and may be related to concomitant use of ICS (51). Physicians should be cautious when using GCs in children: step-down therapy to lower doses when possible and closely monitor children's growth rates.

High-dose GC can induce muscle atrophy and myopathy by direct catabolic effects on skeletal muscle. Symptoms present as proximal muscle weakness and atrophy of the upper and lower extremity muscles. Onset of these symptoms is usually subacute and takes 3 to 4 weeks to resolve after discontinuation of steroids. Moderate exercise has been shown to prevent steroid-induced atrophy (52).

Avascular necrosis is a rare complication of GC use that most commonly affects the femoral head and presents as pain in the affected joint. Although the mechanism underlying this effect is not fully understood, it may be caused by GC-induced venous endothelial cell damage leading to decreased perfusion. Magnetic resonance imaging is the most sensitive method for diagnosis of avascular necrosis. Treatment usually involves rest and lightweight-bearing exercises. If conservative treatment fails, surgical options may be considered (53).

Cataracts, particularly the posterior subcapsular type, and glaucoma have been causally associated with the chronic use of systemic GC (52). Studies examining the effects of ICS and INS failed to show any correlation with use of these medications and subsequent development of eye complications (54).

The principal local adverse effects of GC and ICS therapy include oral candidiasis, dysphonia, throat irritation, and cough. Oral candidiasis and dysphonia appear to be dose dependent. Dysphonia is reported in up to 58% of patients using ICS caused by deposition of the active steroid in the oropharynx leading to local myopathy. These problems are not sufficient reasons to discontinue ICS treatment for most patients, but a reduction to lowest effective dose of ICS is appropriate. A spacer and/or a change to a metered-dose inhaler (MDI) preparation may alleviate oral candidiasis and dysphonia as a result of reduction in drug deposition to the posterior oropharynx (55). Mouth rinsing

after inhalation can also reduce future occurrences. GC-induced candidiasis responds to oral antifungal preparations, such as nystatin or fluconazole.

Allergic reactions to corticosteroids have been reported (56). Topical GC preparations have been implicated in contact dermatitis, a delayed type hypersensitivity reaction, which can be identified through patch testing. Immediate, IgE-mediated reactions to systemic GCs have been described and are more common in aspirin-sensitive asthmatics. Skin-prick tests are used for confirming this rare diagnosis. More commonly implicated GCs include methylprednisolone, prednisone, triamcinolone, and hydrocortisone. Patients who have confirmed allergy to GCs should undergo skin testing and challenge dosing with an alternative preparation, in a different class if possible.

Inhaled Corticosteroids and Asthma

The recognition of asthma as an inflammatory disease has transformed our approaches to treatment. ICS therapy was introduced in the 1970s, initially targeted to patients with severe asthma who required treatment with oral corticosteroids (57). In 1991, the Guidelines for the Diagnosis and Management of Asthma of the National Asthma Education and Prevention Program recommended ICS therapy for patients with both severe and moderate asthma. By 1997, the recommendations also included patients with mild persistent disease, and the third revision of the Expert Panel Report Guidelines in 2007 (EPR-3) states that ICSs are the most consistently effective long-term control medications at all steps of care for persistent asthma in both children and adults, regardless of severity (58).

ICS therapy is the most common controller medication used in the management of asthma. ICS therapy reduces airway hyperresponsiveness and inhibits inflammatory cell migration and activation via suppression of airway eosinophil recruitment, cytokine generation, and release of other inflammatory mediators. ICS have been shown to reduce severity of symptoms, improve asthma control, improve lung function, and may attenuate worsening of lung function in adults over time. ICS also reduce the risk of exacerbations, emergency department visits, hospitalizations, and death due to asthma (58,59).

The EPR-3 guidelines recommend a stepwise approach for the treatment of persistent asthma. The guidelines stress assessing severity and risk before initiating treatment, monitoring asthma control to adjust therapy, emphasizing patient education about medication use and disease triggers, and assessing other comorbid factors contributing to asthma severity. In patients with persistent

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asthma, ICS therapy remains the first-line recommended treatment in patients of all ages, with dosing dependent on severity and risk. These guidelines also recommend initiation of ICS therapy as soon as possible after diagnosis of asthma. Early initiation of ICS has been shown to provide greater improvement in lung function than if delaying treatment by 2 to 4 years. In addition, patients who had an exacerbation while not on ICS had a greater decline in lung function compared to patients on ICS.

Approximately 50% of patients with asthma do not have significant clinical improvement with use of ICS, even at higher doses (60–62). The dose of ICS required to control asthma may vary because of different types and degrees of inflammation, structural changes worsening asthma severity such as airway remodeling, or corticosteroid-insensitive inflammatory pathways. Biomarkers that may be used to predict steroid responsiveness in steroid naïve patients include blood and sputum eosinophils, fraction of exhaled nitric oxide, and urinary bromotyrosine levels (63,64). Smokers and patients with predominantly neutrophilic asthma have decreased responsiveness to ICS therapy (65). It should be noted African American children with severe asthma could have a decreased response to ICS (66).

Inhaled Corticosteroid Preparations

Currently, there are eight ICS preparations clinically approved for the treatment of asthma in the United States that differ in potency, lipophilicity, aqueous solubility, plasma protein binding, and tissue distribution. They include listed in order of potency from high to low: FF dry powder inhaler (DPI), MF DPI, FP DPI, BDP MDI, CIC MDI, BUD DPI, TA MDI, and FL MDI (16,67).

Whereas pharmacodynamic characteristics and lung delivery method determine the clinical efficacy of ICS, pharmacokinetic properties, including oral bioavailability, lung retention, and systemic clearance, determine therapeutic index of the different ICS, as previously discussed. The ideal ICS would have sufficient metabolic stability and receptor affinity at the site of action but have rapid inactivation in the blood and peripheral tissue.

Comparative studies of inhaled GC preparations should be interpreted with caution because study parameters may differ in their methods of measuring adverse effects and their choices of delivery device. Either of these can result in false comparisons. A better method of comparing various ICSs or a single drug in different formulations is the therapeutic index, which is the ratio of desirable and undesirable effects. The relative anti-inflammatory potency of the ICS from

most potent to least potent can be summarized as follows: CIC = FP = MF = FF > BUD = BDP > TA = FL. These findings parallel the therapeutic index of these medications. Pharmacokinetic variables of the inhaled GCs are summarized in Table 35.2.

Clinical Use of Inhaled Corticosteroid Therapy

ICS therapy is recommended as first-line treatment for all patients with persistent asthma, to control the disease. The clinician should, therefore, initiate daily ICS treatment in any patient who requires a β_2-agonist inhaler more than two times per week or uses more than two β_2-agonist canisters per year. The current approach is to start with a dose of ICS corresponding to the asthma severity classification based on the EPR-3 (68) (see Table 35.4 for comparative doses for adults and children (59)). Step-up therapy with additional controller agents and/or a change of device, ICS, or preparation may control symptoms when single ICS therapy is ineffective. A short course of oral systemic GC may also be used to gain faster control particularly for patients with more severe disease. Once control is achieved, the dose should be stepped down to the lowest possible dose necessary for optimal control, which is defined as best/normal lung function and only occasional need for a short-acting β_2-agonist inhaler. Similarly, if high doses fail to control asthma, nonsteroidal controller therapies should be added (62). Dose changes should be gradual, at 3-month intervals or longer.

TABLE 35.4 COMPARATIVE ICS DOSAGE FOR ADULTS AND CHILDREN

DRUG (DOSE PER ACTUATION, µg)	LOW DOSE (µg)	MEDIUM DOSE (µg)	HIGH DOSE (µg)[a]
Adults, Adolescents, and Children >5 y			
Beclomethasone dipropionate (HFA) (40, 80)	50–100	>100–200	>200
Budesonide (DPI) (90, 180)	100–200	>200–400	>400

Budesonide (nebulized) (500)	250–500	>500–1,000	>1,000
Ciclesonide (HFA) (80, 160)	80	>80–160	>160
Flunisolide (HFA) (80)	80	>80–160	>160
Fluticasone furoate (DPI) (100, 200)	NA	100	200
Fluticasone propionate (DPI) (50, 100, 250) (HFA) (44, 110, 220)	100–200 110–220	>200–400 >220–440	>400 >440
Mometasone furoate (DPI) (110, 220) (HFA) (100,200)	110 100	≥220–<440 200–400	≥440 >400
Children 4 y and Younger			
Beclomethasone dipropionate HFA	100	NA	NA
Budesonide pMDI + spacer	200	NA	NA
Budesonide nebulized	500	NA	NA
Fluticasone propionate HFA	100	NA	NA
Ciclesonide	160	NA	NA

[a]High doses of inhaled corticosteroids are not recommended for use in young children and infants.

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; NA, not

Delivery Devices

The type of delivery device plays an important role in determining the amount of drug delivered to the lungs and subsequently the clinical benefit; Chapter 37 reviews delivery devices in more detail. Lung deposition is influenced by the inhalation device, propellant, particle size, that is, mass mean aerodynamic diameter, and by whether the solution is an aerosol or a suspension. Commonly used devices for GC inhalation are the MDI, DPI, and the nebulizer. The dose of drug delivered to the lungs differs between MDIs and DPIs and among devices delivering different ICSs (Table 35.5), so clinicians should consider these differences when choosing a device. Ease of use, cost, and less-frequent dosing are important factors to consider, because they lead to better compliance. In MDIs, which may be either breath activated or pressurized, hydrofluoroalkane (HFA) propellants have replaced chlorofluorocarbon propellants owing to a worldwide mandate. A spacer may be used with HFA-propelled MDIs to reduce oropharyngeal deposition, minimize local side effects, and improve distal drug distribution in the lungs (68). This mechanism, with possible attachment of a face mask, is the delivery method of choice for children (69). Aerosol particle size is also a key determinant of lung deposition and regional distribution of inhaled drugs. Using a pMDI with extra-fine particles can also improve lung deposition.

Nebulizers are used for individuals, such as for infants, young children, and the elderly, who cannot use an MDI owing to coordination, cooperation, or breathing patterns. Compared with MDI or DPI inhalers, nebulizers deliver relatively low doses of GC to the lungs. The characteristics of the face mask, the seal, and the breathing pattern all affect the amount of drug delivered (68).

Dose–Response Considerations

Drug deposition in the lungs may be required for clinical response, but the dose–effect relationship for inhaled GC therapy is not linear. In fact, taking into account individual variability, most of the clinical benefit from inhaled GC therapy is achieved by submaximal doses in adults and children (70–72). That is, patients with mild-to-moderate asthma gain the most benefit from using a low- to moderate-dose ICS. However, there may be a dose-related favorable response of bronchial hyperresponsiveness (73). There is a much steeper dose–response curve for systemic effects, however, so the smaller proportional additional benefits of higher doses must be weighed against the risks in individual patients.

One must also consider the severity of the patient's asthma. Patients with very mild asthma have relatively minimal airflow obstruction and little room for improvement; so low doses potentially provide maximal improvement. Patients with unstable or more severe asthma have significantly greater airflow obstruction and therefore may show a greater response to increasing doses. Similarly, those with severe, steroid-dependent asthma may benefit from high-dose ICS as a systemic steroid-sparing agent (74).

TABLE 35.5 COMPARISON OF DRUG DEPOSITION IN THE LUNGS AMONG INHALER DEVICES

DRUG	FORMULATION	MMAD (μ–M)	PULMONARY DEPOSITION (% OF ACTUATION DOSE)
BDP/BMP	MDI-HFA	1.1	53
BUD	DPI	3.7	34
	nebulized suspension	2.9	10–20
CIC	MDI-HFA	1.1	52
FLN	MDI-HFA	1.2	68
FF	DPI	4.0	22
FP	DPI	5.4	16
	MDI-HFA	2.4–3.2	13–18
MF	DPI	2.2	NA
	MDI-HFA	3.7	

BDP, beclomethasone dipropionate; BUD, budesonide; CIC, ciclesonide; DPI, dry powder inhaler; FF, fluticasone furoate; FLN, flunisolide; FP, fluticasone propionate; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; MF, mometasone furoate; MMAD, mass mean aerodynamic diameter; NA, not available.

Systemic Glucocorticoid Therapy for Acute Exacerbations of Asthma

The EPR-3 recommends classifying asthma exacerbations as mild, moderate, and severe. These guidelines emphasize early recognition of an asthma exacerbation, use of home-based action plans for initiating therapy with short-acting inhaled β_2 agonists, and initiation of systemic GC therapy for asthma exacerbations that are not promptly responsive to therapy with the rescue drugs (68). Higher dose inhaled GCs may benefit children with asthma exacerbations (75). For individuals with more profound symptoms or lung function decline consistent with moderate-to-severe exacerbations, systemic GC treatment should be initiated immediately after recognition of an exacerbation. Systemic GC therapy reduces hospitalization rates, inhaled β_2 agonist requirement, and prevents relapses (76,77), especially in patients at high risk for fatal asthma.

Administration can be via oral, IV, or intramuscular routes; there is no clear evidence to suggest superiority of route of administration. In addition, lower doses (≤80 mg methylprednisolone equivalent) of systemic GC seem as effective as higher doses for initial management of acute asthma (78,79). Oral GCs may be utilized in the outpatient or emergency department setting for treatment of acute exacerbations. Commonly utilized dosing regimens include prednisone 40 to 80 mg/day (1 to 2 mg/kg/day in children, max 60 mg/day) in 1 to 2 divided doses or equivalent doses of an alternate GC (68). The duration of therapy for an exacerbation can be individualized based on severity of exacerbation and patient-specific factors. In general, an asthma exacerbation may require a 3- to 14-day course of systemic GCs (with 5 to 10 days recommended by expert parameters (68)). Tapering is not necessary for courses of GC at or less than 14 days duration. Intramuscular depot injections of GC can be used for individuals with risk of noncompliance. For individuals requiring prolonged treatment for more severe or refractory exacerbations, alternate-day dosing can be utilized to reduce the risk of systemic side effects. The clinician should frequently re-evaluate patients on prolonged steroid courses and attempt to reduce the dose by 5 to 10 mg every 2 weeks until the lowest clinically effective dose is reached. The goal is to discontinue systemic GC therapy if possible.

IV GCs are commonly administered in the emergency department setting, and may include hydrocortisone, betamethasone, methylprednisolone, and dexamethasone. Methylprednisolone, because of its anti-inflammatory potency, lower MC activity, and lower price by comparison with hydrocortisone, may be

the drug of choice for IV therapy. For acutely, critically ill asthmatic adults, IV dosing of methylprednisolone, 60 to 125 mg IV every 6 hours (or its equivalent) may be appropriate (79). Dosing intervals depend on the clinical condition of the acutely ill asthmatic and pharmacokinetic properties of the GC. However, intervals may begin at every 4 to 6 hours. Treatment can be maintained for 48 hours depending on the clinical response. When signs and symptoms improve, doses can be tapered to twice daily, then to a single morning daily dose. Patients who require IV GCs can be switched to oral GCs once stable. The total duration of IV therapy is dependent on both subjective and objective improvement in respiratory status.

Steroid-Resistant or Steroid-Dependent Asthma

GC sensitivity can be affected by bioavailability of the GC preparation, and variability of GC receptors (GCR) and GC receptor transcriptional activity (80). Specifically, reduced numbers of GCRs, altered affinity for the ligand for GCRs, reduced ability of the GCRs to bind DNA, or increased expression of inflammatory transcription factors that compete for DNA binding can reduce cellular responses to GCs. The balance of GCR splice variants may also impact GC sensitivity. GCR-β will not bind to GCs but does interfere with the movement of GCR-α to the nucleus and with gene activation. Increased expression of GR-β has been noted in fatal asthma and nocturnal asthma (81).

In asthmatics, steroid insensitivity is defined as persistent lack of control despite GC therapy, or worsening of asthma on reduction or discontinuation of GCs, and may be driven by some or all of these factors. Insensitivity to GCs may be induced by chronic inflammatory cytokine exposure, or by chronic exposure to corticosteroids (82). Further, some virus-induced inflammatory pathways may induce GC resistance, thereby affecting the ability of GCs to prevent or treat viral-induced asthma exacerbations (83,84). Common characteristics of asthmatics, such as obesity, smoking, and vitamin D deficiency have all been associated with steroid insensitivity in adults (85). Asthma with predominant type 2 inflammation, characterized by eosinophilia and/or atopy, responds to GC treatment better than asthma without type 2 inflammation (63).

Ex vivo measurements of cellular responses to GCs have identified decreased reactivity of peripheral blood mononuclear cells of severe asthmatics, related to histone deacetylase activity (86). Differential responses of alveolar macrophages (87,88) and airway smooth muscle cells (46) to GCs may also contribute to GC insensitivity in severe asthma.

Complete resistance to GCs in asthma is rare. Resistance can be identified by failure to significantly improve forced expiratory volume in 1 second or peak expiratory flow after treatment with prednisone 40 to 60 mg daily for 2 to 3 weeks, or equivalent systemic doses. Intramuscular dosing can address concerns of medication noncompliance. It is also important to determine that the patient has asthma and not another disease, such as chronic obstructive pulmonary disease, which may not respond to GC treatment. The clinician should also investigate the possibility of comorbidities or contributing factors, such as aeroallergen exposure, other medications, or psychologic problems that could increase the severity of asthma and its resistance to treatment.

Some asthma treatments are the so-called "corticosteroid-sparing" drugs because they may reduce GC requirements through addressing additional inflammatory or physiologic effects of asthma. These include immunosuppressants, biologics (anti-IgE (89) and anti-IL-5 (90)), macrolide antibiotics (91), and bronchial thermoplasty (92). These treatments are discussed in Chapters 19, 22, and 38.

Intranasal Glucocorticoids and Allergic Rhinitis

Guidelines for the treatment of both perennial and seasonal allergic rhinitis recommend intranasal GCs as safe and effective therapy. These anti-inflammatory medications have prolonged local action, few local side effects, and few, if any, systemic effects (13). All intranasal GCs act directly on nasal inflammation to reduce the symptoms of allergic rhinitis, including nasal congestion, itching, sneezing, and rhinorrhea. They reduce fluid exudation and the number of circulating inflammatory cells, including basophils, lymphocytes, mast cells, eosinophils, neutrophils, and macrophages. Treatment with intranasal steroids also usually improves ocular symptoms, including redness, itching, and watering. This benefit likely reflects both an overall decrease in the inflammatory mediators and inhibition of ipsilateral and contralateral neural reflex arcs from the nose to the eye (93). Intranasal GC preparations have rapid onsets, short half-lives, and rapid first-pass hepatic metabolism consistent with the ICS.

Intranasal GC therapy is recommended as first-line treatment and the most effective monotherapy for treating perennial and seasonal allergic rhinitis (94). Combination therapy of allergic rhinitis with concomitant use of intranasal GCs with oral antihistamines, intranasal antihistamines, and/or oral leukotriene antagonists may achieve improved symptom control and is therefore common in

clinical practice. Treatment with intranasal GCs is best begun days before allergen exposure when possible—usually about 2 weeks before the beginning of allergy season—and may be maintained for another 2 weeks after the end of the season to control residual mucosal hyperreactivity. However, the onset of action of intranasal steroids may be as early as 3 to 4 hours in some individuals, and is estimated at approximately 12 hours in others. Therefore, some individuals may benefit significantly from as-needed treatment. Others require daily treatment for full benefit. Guidelines recommend tapering the dose to the lowest level required to maintain symptom relief after reaching initial control (94).

Currently, there are multiple intranasal ICS preparations available for treatment of allergic rhinitis in the United States for children and adult (Table 35.6). All have similar safety profiles, and all are similarly efficacious in controlling symptoms. Patient preference for and clinical benefit from intranasal GC may vary among preparations because of mechanism of delivery (spray versus mist versus aerosol), formulation (aqueous versus alcohol), scent, and volume of solution delivered. The nasal spray pump—available with BUD, CIC, FL, FP, MF, and TA—provides solution directly to the nasal cavity, with most solution coating the inferior turbinates (95). Intranasal GC sprays are now available for over-the-counter purchase. A nasal misting device of FF can provide less volume and may be better tolerated by those averse to dripping. Two intranasal aerosol preparations are available in the United States by prescription—CIC and beclomethasone—and were developed to improve the intranasal deposition profile.

Patient instructions for use of intranasal steroid preparations share the same general principles across devices. The patient should blow his or her nose to clear residual mucus. The head should be positioned forward or slightly downward. The administration device should be positioned into each nare with the nozzle directed toward the ipsilateral lateral wall, in the general direction of the ear. This minimizes septal deposition of medication and subsequently the risk of septal irritation. A gentle sniff is allowed, but patients are taught not to inhale strongly as to reduce the rate of posterior oropharyngeal deposition and clearance by swallowing.

Most adverse effects are mild and do not warrant discontinuation of treatment. Epistaxis occurs in 5% to 8% of patients and is usually self-limiting. Atrophy or thinning of the nasal tissue with long-term use is not a problem with the newer intranasal GCs. Oral candidiasis has been reported rarely. The potential for systemic absorption and HPA axis suppression remains a concern

for children and adults. However, studies have generally found no difference between intranasal GCs and placebo in their effects on HPA axis function in either children or adults (96,97). Anticipatory clinical monitoring should be utilized, however, particularly for individuals with a history of HPA axis dysfunction, hepatic dysfunction, or use of medications affecting hepatic metabolism, and those on other topical or systemic steroid preparations.

Corticosteroids for Other Allergic Diseases

Nasal Polyposis

Topical and systemic GCs are accepted medical therapy for patients who have nasal polyposis (98,99). Many patients suffering from nasal polyposis will respond to systemic GC treatment with improvement in symptom scores, polyp scores, and imaging scores. The duration of benefit varies. This so-called "medical polypectomy" may be achieved with a 2-week treatment of oral prednisone, 30 to 50 mg daily with tapering after the first 4 days of treatment. The simultaneous and subsequent use of intranasal steroids is common in clinical practice. Maintenance therapy with intranasal GC preparations, including BDP, BUD, CIC, FL, FP, MF, and TA, have been shown to variably reduce polyp size and prevent regrowth after surgical polypectomy (98).

TABLE 35.6 INTRANASAL STEROID PREPARATIONS (AVAILABLE IN THE UNITED STATES)

DRUG (US BRAND NAME)	DELIVERY TYPE	DOSE SPRAY	USUAL PEDIATRIC ADMINISTRATION, SPRAY(S) PER NOSTRIL (AGE, YEARS)	USUAL ADULT ADMINISTRATION, SPRAY(S) PER NOSTRIL (AGE, YEARS)
Beclomethasone				
QNASL	Aerosol	40 μg	1 daily (4–11)	—
		80 μg	—	2 daily (≥12)
Budesonide				
Rhinocort	Spray	64 μg	1–2 bid (≥6)	1–2 bid (≥12)

Aqua

Ciclesonide

| Omnaris | Spray | 50 | 2 daily (≥6) | 2 daily (≥12) |
| Zetonna | Aerosol | 37 | 1 daily (≥12) | 1 daily (≥12) |

Flunisolide

| Nasarel | Spray | 29 | 1 tid or 2 bid (6–14) | 2 bid or 2 tid (≥14) |

Fluticasone Furoate

| Veramyst | Mist spray | 27.5 | 1 daily (2–11) | 2 daily (≥12) |

Fluticasone Propionate

| Flonase | Spray | 50 | 1 daily (4–11) | 1–2 daily (≥12) |

Mometasone

| Nasonex | Spray | 50 | 1 daily (2–11) | 2 daily (≥12) |

Triamcinolone

| Nasacort | Spray | 55 | 1–2 daily (≥2) | 1–2 daily (≥12) |

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bid, twice daily; tid, three times daily.

Atopic Dermatitis and Allergic Contact Dermatitis

The use of high-potency topical GCs has led to improved treatment for dermatologic conditions that have an inflammatory etiology, such as AD and contact dermatitis (Chapters 29 and 30). AD is a chronic, pruritic, inflammatory skin condition. Management of AD centers on a regimen of excellent skin care (hydration and emollients), antipruritic medications, anti-inflammatory medications, antibacterial treatments, and avoidance of triggers such as allergens or irritants. It is critical for clinicians treating patients with AD to address and emphasize each of these treatment realms (100). For many patients with AD, skin care and allergen avoidance will control their disease. Topical steroids are used on a temporary basis to treat flares of AD in these patients. Other patients will require regular use of topical steroids to maintain adequate control of AD.

There are seven classes of topical corticosteroid, ranked according to potency with class 1 being the most potent. The choice of topical corticosteroid potency depends on the severity and distribution of AD lesions, taking into account surface area and degree of systemic absorption that could lead to HPA axis suppression. Whereas using less potent corticosteroid treatments minimizes side effects, under treatment of the skin inflammation may result in persistence or worsening of AD. A more effective strategy may be to use a stepped approach starting with a mid-potency preparation (except for eczema involving the face, axillae, or groin) and, with clinical improvement, switching to a lower potency preparation for maintenance treatment. Frequent clinical reevaluation is warranted. High-potency corticosteroids may be needed for severe hand and foot eczema, or for short periods of time on other areas of the body, and should not be used on the face, genitalia, or in skin folds. Only mild-to-moderate potency steroid preparations should be used in children. In severe cases of AD, oral GC may be used sparingly. Topical and systemic immunomodulators can be used as steroid-sparing therapy or for those refractory to treatment (100).

Contact dermatitis is a delayed hypersensitivity reaction to topically exposed antigens. Identification and avoidance of the offending antigen is required for management of contact dermatitis (101). In the acute phase, topical and/or systemic GCs can be used to reduce skin inflammation. Severe allergic contact dermatitis that fails to respond to topical treatment may improve with once-daily, then alternate-day oral prednisone at doses of 30 to 60 mg for 1 to 2 weeks (102).

Ocular Allergy

Topical antihistamines and mast cell stabilizers are the typical treatments for

mild-to-moderate allergic conjunctivitis, but in severe cases, topical corticosteroids—preferably those with reduced side effects—may be necessary for temporary use to achieve control of disease or in rare cases, for long-term control (93). Loteprednol etabonate has been found effective for treating ocular allergy and inflammation, and with addition of an ester group to the structure, has an improved safety profile with less impact on intraocular pressure and cataract formation (103). Loteprednol etabonate eye drops are available as either 0.5% or 0.2% suspensions. Several randomized trials confirm that the lower dose is effective in reducing redness and itching without causing significant changes in intraocular pressure, even with long-term use (104).

GCs are also use to treat vernal keratoconjunctivitis, a severe but transient form of ocular allergy, and atopic keratoconjunctivitis, which is a severe allergic conjunctivitis with AD. Both of these disorders have potential for corneal complications and are treated accordingly. Treatments include loteprednol etabonate, fluorometholone 0.1%, and in severe cases, topical immunomodulators such as cyclosporine and tacrolimus (103).

Idiopathic Anaphylaxis and Urticaria and Angioedema

Idiopathic anaphylaxis (IA) is a diagnosis of exclusion that can affect both adults and children. As with other cases of anaphylaxis, treatment of acute attacks of IA includes emergent epinephrine administration with adjunctive antihistamines and systemic GCs. For individuals with frequent episodes of IA, defined as at least two episodes in the preceding 2 months or at least six episodes in the preceding year, systemic GC therapy is used to induce remission. Patients are instructed to take both a daily antihistamine and prednisone 40 to 60 mg by mouth daily for 1 to 2 weeks, until symptom control is achieved. After this time, prednisone can be switched to alternate-day dosing and tapered slowly, by 5 mg every other day, every 1 to 2 weeks. If prednisone dose not achieve symptom control, the diagnosis of IA should be questioned (105).

Acute and chronic urticaria are common conditions. Management of acute and chronic spontaneous urticaria typically includes H_1 and H_2 antihistamines, and in many cases, symptoms can be controlled with these treatments. In the case of acute severe urticaria, or for refractory cases of chronic spontaneous urticaria that persist despite high-dose antihistamine treatment, additional anti-inflammatory measures are needed to control symptoms. Systemic GC therapy can be used for short periods of time to give relief. Initial therapy with GC may start with 30 to 40 mg of prednisone to control symptoms, and if needed for longer term control, alternate-day therapy with a taper as clinically indicated and

tolerated. Omalizumab or systemic immunosuppressants (cyclosporine, tacrolimus, and azathioprine) can be used to control urticaria, as steroid-sparing agents (see Chapter 31). Unique among subtypes of urticaria, delayed pressure urticaria may respond more favorably to topical corticosteroids to control local disease (106).

Eosinophilic Esophagitis

Eosinophilic esophagitis is a chronic, antigen-driven inflammatory disorder characterized by eosinophilic inflammation of the esophagus with resultant esophageal dysfunction. Symptoms can vary and include feeding refusal, abdominal pain, reflux, dysphagia, and food impaction. Although empiric or testing-guided food avoidance measures improve this disease for a significant proportion of patients, some will require medical therapy. A short course of systemic GC therapy can be used in the setting of acute severe symptoms. Topical GC may utilized in this setting to reduce eosinophilia, epithelial fibrosis, and remodeling. Viscous BUD (1 mg for children, 2 mg for adolescents and adults; divided twice daily) and FP (440 to 880 µg for children, 880 to 1,760 µg for adults; divided twice daily) have been studied for this indication (107,108). Patients are instructed to swallow the treatment after a meal, with avoidance of subsequent eating or drinking for 30 minutes (109).

■ CONCLUSIONS

GC therapy is widely used for treatment of allergic inflammatory disease because of the wide range of mechanistic targets and clear therapeutic benefits. Because of the tissue specific and systemic side effects of GCs with regular or high-dose use, health care providers must utilize topical preparations when possible, minimize use to lowest effective dose, and carefully monitor patients for the development of side effects.

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Other Antiallergic Drugs: Cromolyn, Nedocromil, Antileukotrienes, Anticholinergics, and Theophylline

CAROL A. WIGGINS

◾ OVERVIEW

This chapter summarizes the pharmacology, efficacy, and safety parameters of cromolyn and nedocromil, collectively known as cromones; antileukotrienes; anticholinergics; and theophylline. Antihistamines, corticosteroids, and β agonists are discussed elsewhere in this book.

◾ CROMOLYN AND NEDOCROMIL

Cromolyn and nedocromil are chemically dissimilar drugs with similar pharmacologic and therapeutic properties. They are weak anti-inflammatory drugs without significant adverse effects. These drugs have been replaced by more potent anti-inflammatory drugs as first-line therapy (1,2), but may play an adjunctive role in the treatment of asthma, allergic rhinitis, and conjunctivitis (Tables 36.1 and 36.2).

Pharmacology

Cromolyn and nedocromil have low oral bioavailability, and all of their pharmacologic effects results from topical deposition in the lung or on mucosal surfaces. Cromolyn has a very short plasma half-life of 11 to 20 minutes (3). Nedocromil has a longer half-life of 1.5 to 2 hours (4). There are no significant drug interactions with the cromones (3,4). Neither drug relieves bronchospasm, both should be used preventatively, as maintenance therapy, or prior to exercise or allergen exposure (1–3).

Mechanism of Action

The cromones block chloride transport channels in airway epithelial cells, neurons, and mucosal mast cells that appear to result in their anti-inflammatory

effects (5–8). Cromolyn and nedocromil have been shown to inhibit mediator release from mast cells (7,8), immunoglobulin E synthesis (9,10), and to suppress eosinophil chemotaxis and survival (11) as well as neutrophil activation and migration (12). They also cause release of Annexin A1 (13).

Inhalation challenge studies have determined that cromones equally inhibit both the early- and late-phase asthmatic reactions when administered prior to allergen challenge (14–17). The cromones do not inhibit bronchospasm induced by histamine or methacholine (18–20).

TABLE 36.1 MAINTENANCE DRUGS LISTED IN NHLBI/NAEPP 2007, GINA 2016 REPORTS

AGE (y)	MEDICATIONS: ALTERNATIVES TO INHALED CORTICOSTEROIDS	ALTERNATIVES TO LABA AS ADD-ON THERAPY
0–4	Cromolyn, montelukast	Montelukast
5–11	Cromolyn, nedocromil, LTRA, theophylline	LTRA, theophylline
>11	Cromolyn, nedocromil, LTRA, theophylline	LTRA, theophylline, zileuton, tiotropium[a]

GINA, Global Initiative for Asthma; LABA, long-acting β agonist; LTRA, leukotriene antagonist; NAEPP, National Asthma Education and Prevention Program; NHLBI, National Heart, Lung, and Blood Institute.

[a]Tiotropium approved for age 18 years and older in the United States.

TABLE 36.2 CHARACTERISTICS OF OTHER ANTIALLERGIC DRUGS

DRUG	MECHANISM OF ACTION	SAFETY	EFFICACY	DOSING: ADULTS (A) CHLDREN (C)	DRUG INTERACTIONS
Cromolyn	Blocks chloride	Virtually no known side	Inhibits early and late phase	A and C: 1 ampule (20	None reported

	transport channels in mast cells	effects	of allergic asthma Nonallergic asthma Exercise-induced asthma Systemic mastocytosis Allergic conjunctivitis, vernal conjunctivitis, giant papillary conjunctivitis Allergic rhinitis	mg) qid By nebulizer; 1 ampule (100 mg) 4 times daily 4% solution to be used 1 drop in each eye 4–6 times a day 5.2 mg/spray 1 spray in each nostril 3–6 times a day	
Nedocromil	Blocks chloride transport	None known	Allergic conjunctivitis	2% solution 1 drop in each eye 2 times a day	None reported
Montelukast	Blocks cysteinyl leukotriene receptor	Associated with eosinophilic granulomatosis with polyangiitis (EGPA)/Churg–Strauss syndrome (rare)	Asthma Exercise-induced asthma Allergic rhinitis	C: 6 mo–5 y 4 mg granules to be taken at bedtime; 2–5 y 4 mg chewable tablets; 5–15 y 5 mg chewable tablets. A: 15 y and older 10 mg tablets	None reported
Zafirlukast	Blocks cysteinyl leukotriene	EGPA (rare) Hepatic dysfunction	Asthma	C: 5–11 y 10 mg bid Ages 12 y	Increases warfarin half-life and INR

	receptor	(rare)		and older: 20 mg bid	
Zileuton	Inhibits 5-lipoxygenase activity	Increases liver enzymes in 3%; monitoring of liver enzymes required	Asthma	C: older than 12 and A: 600 mg qid; Sustained-released 600 mg 2 bid	Increases serum levels of warfarin, theophylline, cymbalta, and propranolol
Ipratropium	Anticholinergic	Dry mouth, bad taste; urinary retention, uncommon; glaucoma, blurred vision, dilated pupil, usually after direct contact with the eye, rare	Acute asthma exacerbations in combination with short-acting β agonists; for relief of asthma symptoms in patients intolerant to short-acting β agonists; for asthma induced by β blockers COPD Allergic rhinitis Nonallergic rhinitis; colds	MDI/HFA A: (17 mcg) 2 inhalations 4 times a day as needed for COPD Nebulizer solution C: <6 y 0.25 mg every 20 min for 3 doses for acute exacerbations C: <12 y 0.25–0.5 every 20 min for 3 doses for acute exacerbations then every 4–6 h as needed C: >12 y use adult dosing A: 0.5 every 20 minutes for 3 doses for acute exacerbations then every 4–6 h as needed	None known

				Combination solution with albuterol (0.5/2.5 mg) for nebulizer	
				C>13 y and A: 1 ampule (3 mL) every 20 minutes for 3 doses for acute exacerbations, then every 4–6 h as needed	
				Combination with albuterol (Respimat)	
				A:1 inhalation every 4 hours as needed for COPD	
				Nasal spray	
				0.03% and 0.06% C >5 and A; 2 sprays in each nostril 2–4 times a day for rhinorrhea	
Tiotropium	Anticholinergic	Dry mouth; urinary retention, ocular effects	Asthma COPD	Dry powder inhaler 18 μg qid	None known
				MDI 1.25, 2 inhalations qid for asthma	
				MDI 2.5, 2 inhalations qid for COPD	
Theophylline	Not known Inhibits	Narrow therapeutic	Asthma COPD	All ages: dosage must	Many (including,

phosphodiesterases, antagonizes adenosine receptors, relaxes smooth muscle	index Nausea and headache common Serious adverse effects, including seizures and arrhythmias, causing death have been reported	be individualized based on monitoring peak serum theophylline levels	but not limited to): adenosine, allopurinol, cimetidine, ciprofloxacin, erythromycin, estrogen, fluconazole, fluvoxamine, interferon, lithium, mifepristone, phenobarbital, phenytoin, propranolol, rifampin, ticlopidine, riociguat, verapamil

bid, twice a day; COPD, chronic obstructive pulmonary disease; INR, international normalized ratio; MDI, metered-dose inhaler; qid, once daily.

Efficacy

Cromones are an alternative initial therapy for mild persistent asthma (1,2). Their excellent safety profile may be very appealing to parents or patients who are concerned about side effects of inhaled corticosteroids. Both cromolyn and nedocromil have been reported to improve clinical outcomes and lung function when started early in the course of therapy (17).

Cromones are less efficacious than corticosteroids in the treatment of asthma (18) and have a very limited role in the long-term treatment of asthma (1,2). Although the National Asthma Education Prevention Program 2007 (NAEPP) and Global Initiative for Asthma 2016 (GINA) guidelines suggest that cromones may be useful as prophylaxis prior to exercise or allergen exposure (1,2), cromolyn is only available in the United States as a nebulizer solution for asthma, and nedocromil is not available in any form for inhalation in the United States.

Safety and Drug Interactions

Cromolyn and nedocromil have no known drug interactions, toxicity, or

clinically significant adverse effects.

Dosing and Preparations

Cromolyn is available in 20 mg/mL ampoules for nebulization to be administered four times daily, or 10 to 60 minutes prior to allergen exposure for ages 2 years and older.

Cromolyn is available as a 100-mg ampoule to be taken orally for gastrointestinal symptoms of systemic mastocytosis for infants, children, and adults; the recommended dosage for mastocytosis is discussed elsewhere in this book.

Cromolyn is available as a nasal spray for ages 2 years and older to be used as one spray in each nostril three to six times a day.

Cromolyn is available as a 4% ophthalmic preparation to be used four to six times a day for allergic conjunctivitis, giant papillary conjunctivitis, vernal keratitis, and vernal keratoconjunctivitis. Nedocromil is available as a 2% ophthalmic preparation approved to be used twice a day for allergic conjunctivitis.

■ ANTILEUKOTRIENES

The leukotrienes C_4, D_4, and E_4, previously identified as the "slow reacting substance of anaphylaxis," are potent mediators of inflammation in asthma. The antileukotrienes available in the United States are montelukast, zileuton, and zafirlukast. The GINA and NAEPP guidelines suggest antileukotrienes as an alternative "STEP 2" to low-dose inhaled corticosteroid therapy for children and adults with asthma (1,2). The NAEPP guidelines suggest antileukotrienes as an alternative "STEP 2" in asthmatic smokers (1).

Leukotriene Formation and Biologic Activity of the Leukotrienes

The leukotrienes are formed from arachidonic acid. The initial steps in this process are catalyzed by an enzyme complex containing 5-lipoxygenase (5-LO). Separate pathways lead to production of leukotriene B_4 (LTB$_4$) or the cysteinyl leukotrienes, such as leukotriene C_4 (LTC$_4$), leukotriene D_4 (LTD$_4$), and leukotriene E_4 (LTE$_4$) (20).

The cysteinyl leukotrienes have a common receptor that is distinct from the

LTB$_4$ receptor. The cysteinyl leukotrienes are potent mediators of bronchoconstriction, airway hyperresponsiveness, microvascular permeability, and mucus secretion. LTB$_4$ is a chemoattractant for neutrophils in the lung (21).

The leukotrienes are important mediators of aspirin-exacerbated respiratory disease. Aspirin-sensitive asthmatics have increased baseline levels of leukotrienes compared with nonaspirin-sensitive asthmatics, and develop markedly enhanced levels of leukotrienes in their lungs, nasal secretions, and urine following aspirin challenge (22).

Mechanism of Action of Antileukotrienes

Zileuton directly inhibits the catalytic activity of 5-LO and inhibits production of LTB$_4$ as well as the cysteinyl leukotrienes. Zafirlukast and montelukast are competitive antagonists of the cysteinyl leukotriene receptor and, therefore, inhibit the activity of LTC$_4$, LTD$_4$, and LTE$_4$ (21). The antileukotrienes have been shown to inhibit influx of eosinophils into the airways and reduce blood eosinophil levels (22–24). Montelukast and zafirlukast have demonstrated bronchodilator activity (21,23).

Montelukast and zafirlukast inhibit both the early- and late-phase response to allergen (25,26). Zileuton does not significantly inhibit airway response to allergen (27). The antileukotrienes have demonstrated protective effects against exercise-induced bronchoconstriction (28). Zafirlukast and zileuton inhibit bronchoconstriction induced by cold dry air (29,30). Zafirlukast inhibits sulfur dioxide-induced bronchospasm (31). Zileuton and montelukast have been shown to inhibit aspirin-induced bronchospasm in aspirin-exacerbated asthma (32).

Efficacy

The antileukotrienes result in fewer asthma symptoms and exacerbations, decreased use of rescue inhalers and oral corticosteroids compared to placebo. They are less efficacious than inhaled corticosteroids (21,32,33), but may be suitable as monotherapy for selected patients or as add-on therapy to inhaled corticosteroids (1,2).

Antileukotrienes may result in improved asthma control as additional therapy in patients not adequately controlled by inhaled corticosteroids. Most of the data from randomized trials show that long-acting β agonists are superior to antileukotrienes as add-on therapy to inhaled corticosteroids for asthma (34).

Montelukast and zafirlukast have been shown to be similar in efficacy and

tolerability to antihistamines for allergic rhinitis (35,36). Fluticasone propionate has been shown to be superior to montelukast for the treatment of allergic rhinitis (37).

Safety and Drug Interactions

The antileukotrienes are generally safe and well tolerated.

Zileuton can cause hepatotoxicity as well as elevated transaminases, hepatitis, and death from liver disease. The manufacturer's surveillance studies have reported elevated transaminases occurring in 1.8% to 3.2% of patients. Patients should have baseline alanine transaminase measured and then monthly for 3 months, then every 2 to 3 months for the first year, and at the doctor's discretion thereafter (38). Montelukast and zafirlukast do not have known hepatotoxicity at recommended doses.

Montelukast and zafirlukast have been associated with the development of eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg–Strauss syndrome. Many of the patients who developed EGPA were severe asthmatics who had previously received oral steroids, and the manifestations of vasculitis developed after systemic steroids were reduced or discontinued (39). However, a study of 24 EGPA patients revealed that the six patients who developed EGPA while taking montelukast were taking oral steroids when signs of EGPA developed (40).

Zileuton and zafirlukast may prolong the international normalized ratio in patients taking warfarin. Zileuton significantly inhibits the hepatic metabolism of theophylline, and may result in theophylline toxicity; zafirlukast may also increase theophylline serum levels. Zileuton has many drug interactions, and caution is advised when prescribing it along with other drugs that are metabolized by the liver (38,41).

Dosage and Preparation

Zileuton is approved for individual aged 12 years and older and is available as a 600-mg tablet to be taken four times daily, or a 600-mg sustained-release tablet to be taken as two tablets twice daily with food. Zafirlukast is approved for ages 5 years and older; it is available in 10 mg tablets for ages 5 to 11 and 20 mg tablets for ages 12 and older to be taken every 12 hours. Montelukast is available as 4 mg granules for ages 6 months to 5 years, 4 and 5 mg chewable tablets for ages 2 to 6 and ages 6 to 15 years, respectively, and 10 mg tablets for ages 15 years and older. Montelukast is administered once a day, in the evening or 2

hours prior to exercise. Zileuton is approved for ages 12 years and older; it is available as 600 mg tablets to be taken 1, four times daily or as a 600-mg sustained-release tablet to be taken 2 twice daily.

■ ANTICHOLINERGICS

The naturally occurring anticholinergic alkaloids, such as atropine, have been recognized for centuries to have beneficial effects in asthma. The toxicity of atropine gave rise to the mnemonic: red as a beet; hot as a hare; dry as a bone; blind as a bat; and mad as a hatter. The useful properties of atropine led to the development of inhaled anticholinergics with minimal systemic absorption and side effects.

Ipratropium was the first anticholinergic to be approved by the Food and Drug Administration for relief of acute asthma symptoms and is also available as a nasal spray. Tiotropium is approved as a maintenance treatment for asthma.

Cholinergic Mechanisms in the Airways

The vagus nerve supplies autonomic innervation to the large- and medium-sized airways. Release of acetylcholine from the parasympathetic postganglionic fibers acting on muscarinic receptors, results in smooth muscle contraction and release of secretions from submucosal glands. The activity of cholinergic fibers results in a constant low level of tonic activity of the airways. A variety of stimuli, including irritants, exercise, cold dry air, histamine, and allergens, can trigger irritant receptors of vagal afferent nerves, resulting in almost immediate reflex bronchoconstriction and mucus hypersecretion (42).

Mechanism of Action of Anticholinergics

The anticholinergic agents compete with acetylcholine at muscarinic receptors. Because muscarinic receptors are found primarily in the central airways, anticholinergic bronchodilatation occurs mostly in the larger airways. The anticholinergics provide virtually complete protection against bronchoconstriction by methacholine. Anticholinergics provide varied protection against bronchoconstriction induced by other stimuli, including histamine, irritants, exercise, and allergens (43).

Pharmacology

Atropine is well absorbed from mucosal surfaces and reaches peak serum levels within 1 hour. The bronchodilatory effects last for 3 to 4 hours. Atropine relaxes

smooth muscle in the airway, gastrointestinal tract, iris, and peripheral vasculature. It inhibits relaxation of the urinary sphincter. It causes bradycardia at low doses and tachycardia at high doses. It reduces salivary secretions and mucociliary clearance in the airways. Atropine crosses the blood–brain barrier and can cause significant central nervous system side effects (44).

Ipratropium and tiotropium are quaternary ammonium derivatives of atropine. The quaternary structure allows for poor absorption across respiratory and other membranes and results in fewer systemic side effects than atropine. Ipratropium starts to work within 15 to 30 minutes after inhalation, but maximum bronchodilatation may not result until 90 minutes; effects last up to 6 hours (45). Tiotropium has a peak onset of dilatation within 1 to 3 hours and effects last for more than 24 hours (46).

Efficacy

Anticholinergics are less effective bronchodilators and have a much slower onset of action than albuterol which has its peak effect within 5 to 15 minutes (46). Current guidelines do not recommend anticholinergic medications as standalone treatment for asthma (1,2). Ipratropium may be useful as a bronchodilator in patients who are intolerant to short-acting β agonists (47). Tiotropium has been shown to improve symptoms and lung function when used as add-on therapy in patients with difficult to control asthma (48,49). Ipratropium has been shown to reduce hospital admissions when added to short-acting β agonists in the acute treatment of asthma exacerbations (47). Ipratropium is recommended for the treatment of bronchospasm caused by β blockers (1). Anticholinergics are included in NAEPP and GINA guidelines to be used in addition to short-acting β agonists for the treatment of acute, severe asthma exacerbations (1,2).

Ipratropium bromide nasal spray relieves rhinorrhea associated with allergic or nonallergic rhinitis (50,51) as well as rhinorrhea caused by viral upper respiratory infections (52).

Safety and Drug Interactions

Atropine causes significant side effects, even at therapeutic doses. Dry mouth, warmth and flushing of the skin, impairment of mucociliary clearance, gastroesophageal reflux, and urinary retention are common. Central nervous system effects ranging from irritability to hallucinations, and coma may occur. Tachyarrhythmias may occur at low doses, and atrioventricular association may occur at high doses. Atropine may trigger acute angle-closure glaucoma.

Because of the availability of drugs with superior safety and efficacy, there is no longer a role for the use of atropine in the treatment of asthma; it is used to treat bradycardia and organophosphate poisoning (44).

Ipratropium bromide is very well tolerated and has little toxicity because it is so poorly adsorbed. Rare cases of blurred vision, papillary dilatation, and angle-closure glaucoma have been reported when the drug has had direct contact with the eye. Urinary retention may occur, particularly in men with prostatic hyperplasia. Dry mouth and a bad taste are common side effects with anticholinergics. Paradoxic bronchospasm has rarely been reported (46).

Tiotropium is also generally safe and well tolerated, but because its half-life is long, ocular and urinary side effects may occur. There is a concern that the mist formulation of tiotropium, but not the dry powder formulation, may be associated with increased mortality (46,53), but a recent large multicenter trial comparing the two devices failed to demonstrate increased deaths in patients using the mist device (54).

Dosage and Preparation

Ipratropium is available as a metered-dose inhaler to be used up to four times a day. It is available as a 0.25-mg nebulizer solution for children younger than 6 years or a 0.5-mg solution for individuals aged 6 years and older to be administered every 4 to 6 hours, or every 20 minutes for three doses in combination with a β agonist for acute asthma exacerbations. Ipratropium is also available in 2.5 mg solution in combination with 0.5 mg of albuterol for the treatment of adults and children with acute asthma exacerbations. Ipratropium is also available as a nasal spray 0.03% for allergic or nonallergic rhinitis and 0.06% for colds to be used two to three times a day.

Tiotropium is available in two devices for adults aged 18 years and older. An 18-mg dry powder capsule is administered once daily by the Handihaler device. A metered-dose inhaler is available in 1.25 and 2.5 µg formulations per actuation to be administered two inhalations once a day. Only the 1.25-dose is approved for the treatment of asthma.

◼ THEOPHYLLINE

Theophylline was initially used as a diuretic; it was first used to treat acute asthma in the 1930s and was one of the first drugs to be used as maintenance therapy for asthma. Emphasis on the treatment of inflammation in asthma as well as the development of drugs with similar or superior safety and efficacy and

improved safety and tolerability has led to a decline in the use of theophylline (55). Theophylline is listed as an alternative maintenance drug and as add-on therapy in the NAEPP and GINA guidelines (1,2).

Pharmacology

Theophylline is a methylxanthine, similar in to the naturally occurring xanthenes caffeine and theobromine. The solubility of methylxanthines is low unless they form salts or complexes with other compounds such as ethylenediamine (as in aminophylline). Theophylline is rapidly absorbed after oral or rectal administration and maximum serum levels occur 2 hours after ingestion on an empty stomach. Food generally slows the rate, but not the amount of absorption (55).

The elimination rate of theophylline varies widely among individuals depending on age, genetic and environmental factors as well as underlying disease. It is metabolized by the cytochrome P450 system of the liver, and serum levels are altered by many medications, which are discussed in detail later in this chapter. High-protein, low-carbohydrate diets and diets high in charcoal-grilled foods as well as smoking tobacco and marijuana increase theophylline clearance and may decrease theophylline levels. Pregnancy, fever, advanced age, liver disease, congestive heart failure, and chronic obstructive pulmonary disease (COPD) with hypoxia may increase theophylline levels (56).

Mechanism of Action

The mechanism of action of theophylline is not clearly understood. Theophylline inhibits cyclic adenosine monophosphate–specific phosphodiesterases at high concentrations, but this effect is negligible at therapeutic doses (55). Antagonism of adenosine receptors has also been proposed as mechanism of action of theophylline, and may account for its severe adverse effects, including seizures and arrhythmias. Theophylline activates histone deacetylases, an effect that is most pronounced when their activity is reduced by oxidative stress. This effect is most important in patients with COPD (55). The clinical effects of theophylline are relaxation of smooth muscle in airways, increased respiratory drive, decreased fatigue of respiratory muscles, increased mucociliary clearance, and decreased microvascular leakage into airways (55). Theophylline has been shown have modest anti-inflammatory effects: it reduces the influx of eosinophils and activated CD4^{+} and CD8^{+} T cells into airways (57,58) and reverses steroid resistance in COPD (59).

Theophylline inhibits bronchial hyperresponsiveness to methacholine; it inhibits the early-phase but not the late-phase response to inhaled allergen (1,57).

Efficacy

Theophylline is similar in efficacy but less well tolerated than long-acting inhaled β agonists for the treatment of asthma (60). Comparison studies of theophylline with the long-acting β agonists, formoterol and salmeterol, showed that theophylline provided similar improvement in forced expiratory volume in 1 second, but less improvement in morning and evening peal flow rates and use of rescue inhalers. There were also more adverse events associated with use of theophylline than with use of formoterol or salmeterol (60). A study comparing the leukotriene antagonist zileuton with theophylline found that zileuton was as effective as theophylline and had fewer side effects (61). Theophylline may be an option for asthmatic smokers who do not respond well to inhaled corticosteroids (55).

Safety and Drug Interactions

Theophylline is a drug with very narrow margin of safety. Serum concentrations should be monitored and maintained between 5 and 15 µg/mL; many patients will obtain clinical benefit at serum levels in the low therapeutic range (46). Many common drugs can double or triple serum theophylline levels. Fatal toxicity can occur when levels exceed 25 µg/mL. In a 10-year prospective study of the Massachusetts Poison Control Center, there were 356 cases in which the theophylline level was greater than 30 µg/mL. In all, 74 patients had arrhythmias, 29 had seizures, and 15 subjects died (62). Other toxic effects of theophylline include hypokalemia, hyperglycemia, encephalopathy, hyperthermia, and hypotension (55).

Theophylline has also unpleasant side effects that many patients find intolerable. Headache, irritability, nausea, and insomnia may occur even when serum levels are within the therapeutic range.

Drugs that significantly elevate theophylline levels include clarithromycin, erythromycin, most of the quinolone antibiotics, cimetidine, disulfiram, estrogen, fluvoxamine, interferon-α, pentoxifylline, propafenone, propranolol, tacrine, ticlopidine, thiabendazole, verapamil, and zileuton. Theophylline may decrease the effects of adenosine, diazepam, flurazepam, lithium, and pancuronium. Carbamazepine, phenobarbital, phenytoin, rifampin, and sulfinpyrazone may decrease theophylline levels (55,56).

Preparations and Dosing

Theophylline is usually prescribed in long-acting tablets or capsules, which come in a number of different dosages, to be administered once or twice a day. It is also available as uncoated tablets, encapsulated sprinkles, in suspension, and as a rectal suppository.

The dosage of theophylline is based on the body weight. For children older than 6 months and adults, the starting dose should be 10 mg/kg up to a maximum initial dose of 300 mg/day. The dosage may be increased every 3 days, if tolerated, up to 16 mg/kg with a maximum dose of 600 mg/day. A serum level should be measured after at least 3 days at the maximum dose. The peak serum level occurs 8 to 13 hours after the sustained-release preparations and should be 5 to 15 µg/mL. Dosage requirements generally maintain stable, but concomitant medications and acute or chronic illness may alter serum levels (55).

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Delivery Devices for Inhaled Medications

THEODORE M. LEE AND UMBREEN S. LODI

Inhalation of drugs provides direct delivery for local treatment of bronchial diseases, with more rapid onset of effect and less potential unwanted systemic effects than oral administration. It is estimated that over 450 million inhaler devices are used annually worldwide (1). This chapter primarily focuses on issues relevant to inhalation delivery devices utilized in the treatment of asthma in the United States.

HISTORY OF INHALATION THERAPY

Inhalation therapy for bronchial disorders has been used since ancient times. Centuries ago, the *stramonium* (a botanically derived antimuscarinic agent) cigarette was described as a treatment for acute asthma (2,3). In the 19th century, inhalation devices were developed primarily for use in the treatment of various conditions including tuberculosis, including atomizers which utilized pressure pumps or steam to disperse liquid medication. A UK patent was filed for the first known dry powder inhaler (DPI) in 1864 (4). Antecedents of contemporary inhalation therapy for asthma are grounded in the early part of the 20th century with invention of hand-powered (5) and electrical (6) devices for nebulization of adrenal extract, later, adrenalin solutions. Inhalation therapy subsequently was revolutionized by the introduction of pressurized metered-dose inhaled (pMDIs) containing isoproterenol or epinephrine into clinical practice in the 1950s (7). The first modern DPI, containing cromolyn sodium, was launched in 1967; pMDIs containing albuterol were first marketed in Europe in 1969, followed by beclomethasone dipropionate in 1972 (4,8). pMDIs utilized Freon chlorofluorocarbon (CFC) propellants until the mid-2000s, when these were eliminated because of their roles in depletion of the stratospheric ozone layer (1,9). The phaseout of CFCs stimulated research in innovative aerosol delivery techniques culminating in the development of new propellants and improved

pMDI designs as well as novel DPIs (10,11).

Inhalation devices in use today include conventional pMDIs (used with or without spacer devices), DPIs, and nebulizers. The SoftMist Inhaler (Boehringer Ingelheim), a unique spring-powered device which quickly aerosolizes metered doses of concentrated medications (12), represents an additional category of inhaler device recently launched in the United States.

AEROSOL PARTICLE CHARACTERISTICS

An understanding of the fundamentals of particle behavior in inhalation therapy is required for informed use of aerosol devices in the clinical management of asthma. Deposition of aerosolized particles occurs primarily as a result of inertial impaction, sedimentation, and diffusion; in some instances, turbulent mixing, interception, and electrostatic precipitation may also be additional significant factors (Table 37.1) (13). Figure 37.1, based on scintigraphic data from human subjects for 1.5 mm to 6.0 µm particle sizes (extrapolated for smaller particle sizes) and Fig. 37.2, based on mathematical models, demonstrate the relationship between aerodynamic size of inhaled particles and sites of deposition.

Spatial distribution of deposited particles is strongly affected by particle size. Large particles (>6 µm) tend to mainly deposit in the upper airway, limiting the amount of drugs that can be delivered to the lung, and in the case of corticosteroid preparations, contribute to oropharyngeal adverse effects; when drugs with gastrointestinal (GI) absorption are used, the portion swallowed after deposition in the upper airways also contributes to undesired systemic effects (13). Most submicron (<1 µm) particles are exhaled, and those which are not exhaled deposit mainly in the alveolar region and are systemically absorbed. Based on these considerations, it is generally accepted that particles in the size range 1 to 6 µm are best suited to treat the central and small airways, sites pertinent in therapy of asthma (14).

TABLE 37.1 MECHANISMS OF AEROSOL PARTICLE DEPOSITION

MODE OF CAPTURE	DESCRIPTION OF MECHANISM
Impaction	Particles caught at apex of flow bifurcation due to inertia
Sedimentation	Particles "rain out" from suspension in gas because of gravity

Diffusion	Particles collide with surrounding tissue as a result of Brownian motion
Turbulent mixing	Irregular flow fluctuations result in deposition on airway walls
Interception	Elongated particles impact on airway walls due to their shape and size
Electrostatic precipitation	Charged particles cling to airway walls
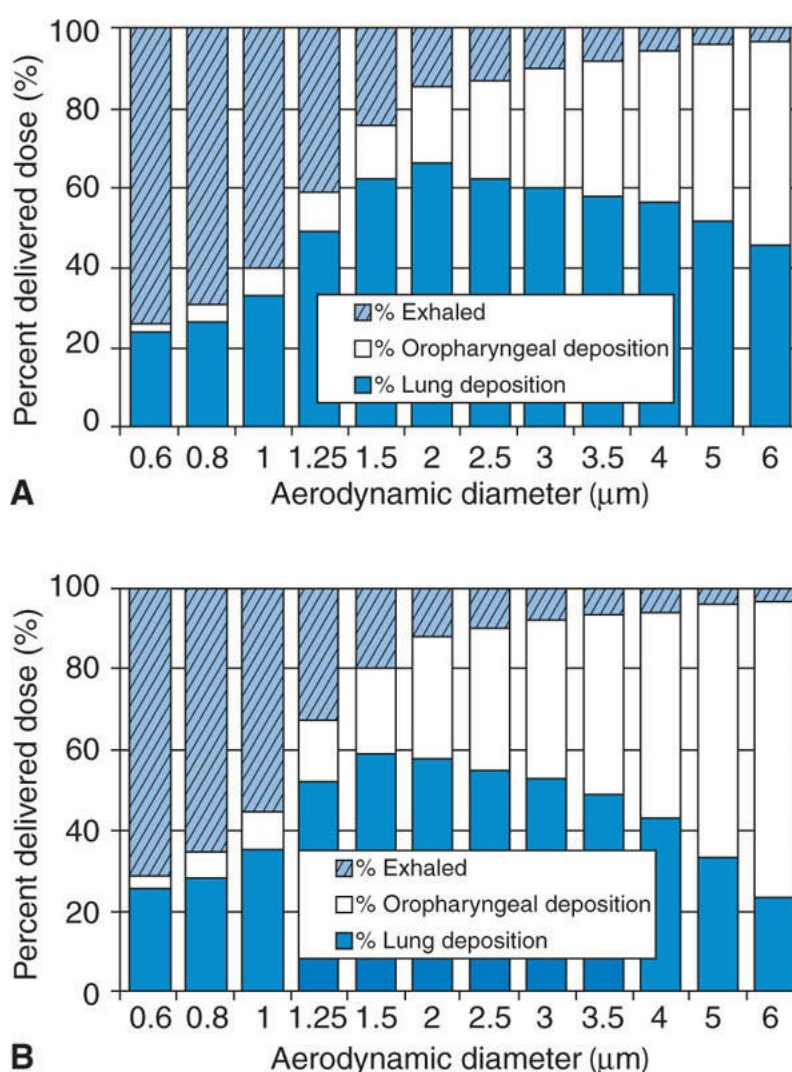
■ **FIGURE 37.1** Aerosol losses caused by oropharyngeal deposition and exhalation as a function of the particle diameter for slow (31 L/minute) (**A**) and fast (67 L/minute) (**B**) inhalation. The figures are based on the experimental data of Usmani et al. (1.5 to 6 µm) (18) and extrapolated data for the particle size

range 0.6 to 1.5 µm. (From de Boer AH, Gjaltema D, Hagedoorn P, et al. Can 'extrafine' dry powder aerosols improve lung deposition? *Eur J Pharm Biopharm*. 2015;96:143–151; with permission.)

Emitted particles from an inhaler device are not of a uniform size. The term *mass mean aerodynamic diameter* (MMAD)—by mass, the diameter at which 50% of the generated particles are larger and 50% are smaller—is used to describe the distribution of particle size produced by an aerosol delivery device. *Fine particle fraction* generally indicates the percentage of emitted particles with MMAD < 5 µm; extra-fine particle fraction generally denotes the percentage with MMAD < 2 µm. Published particle sizes for several inhaler devices are shown in Table 37.2. When interpreting such data, however, it is important to recognize that delivered particle sizes are not static. MMAD may be decreased by high inhalation flow rates (15) and increased by high relative humidity; increasing temperature resulted in indications of reductions in MMAD and increased pulmonary deposition of solution pMDIs in an *in vitro* model, with generally no effect on deposition of a suspension pMDI (16). It has been suggested that dependent on such factors, MMAD may vary around 50% (15) challenging a firm ≤2 µm cutoff definition of extra-fine formulations (17). Also, some available DPIs with MMAD generally in the fine particle range may generate a clinically proportion of their output in the extra-fine range (14).

In some instances, total lung deposition *per se* may be an unreliable predictor of clinical response; it is also necessary to assess regional deposition at relevant sites (e.g., conducting airways versus alveoli) to predict clinical effectiveness (13). Optimal deposition site and particle size for delivery to the targeted area may differ between β-agonist and corticosteroid aerosols. While a 6-µm monodisperse (homogeneous particle size) albuterol aerosol produced increase in forced expiratory volume in 1 second (FEV_1) significantly superior to that from a 1.5-µm monodisperse albuterol aerosol (18), evidence from clinical trials and observational studies suggests that extra-fine particle sizes may be generally desirable for corticosteroid aerosols. Clinical asthma control outcomes with extra-fine particle size corticosteroid inhalers may significantly surpass those achieved with larger size particle preparations (19–23). Extra-fine particle size corticosteroid preparations first emerged during the development of hydrofluoroalkane (HFA) alternatives to CFC propellants. It was found that beclomethasone dipropionate, in suspension in CFC vehicles, was soluble in the HFA propellant, with the solution producing extra-fine aerosols which required lower dosages than CFC beclomethasone to achieve similar clinical effects (24). Explanations for these findings have included longer suspension of the aerosol

prior to inhalation in patients with suboptimal inhaler technique, improved penetration into partially obstructed airways, and a greater clinical role for distal inflammation in asthma than had been previously supposed (19). Extra-fine aerosols may be particularly desirable in pediatric patients with small airways (17). In conjunction with particle size, breathing pattern is also an important factor influencing the extent and site of drug deposition (18) (Fig. 37.1).
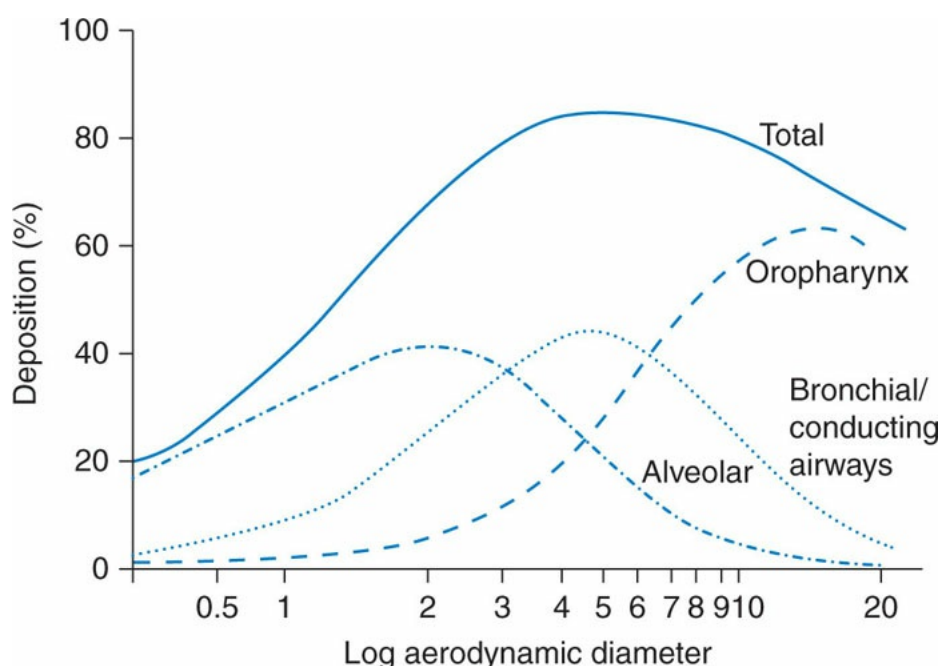
■ **FIGURE 37.2** Relationship between aerodynamic diameter of aerosol particles and sites of deposition. (From Laube BL, Janssens HM, de Jongh FH, et al. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J*. 2011;37:1308–1331; data from Köbrich R, Rudolf G, Stahlhofen W. A mathematical model of mass deposition in man. *Ann Occup Hyg*. 1994;38:15–23, with permission.)

TABLE 37.2 MASS MEDIAN AERODYNAMIC DIAMETER (MMAD) (µM) OF PARTICLES DELIVERED FROM INHALER DEVICES

DPIs	
Diskus (fluticasone propionate dry powder)	5.4
Turbuhaler (budesonide dry powder)	4.0
Spiromax/Respliclick (budesonide + formoterol dry powder)	2.5

Ellipta (fluticasone furoate + vilanterol dry powder)	2.3

HFA pMDIs

Suspension formulations

Fluticasone propionate HFA pMDI	2.4
Fluticasone propionate + formoterol HFA pMDI	3.2

Solution formulations—extra-fine particle

Ciclesonide HFA pMDI	1.1
Beclomethasone dipropionate HFA pMDI	1.1
Flunisolide HFA pMDI	1.2

Respimat SMI

Tiotropium	3.7

DPIs, dry powder inhalers; HFA, hydrofluoroalkane; pMDIs, pressurized metered-dose inhalers; SMI, Soft Mist Inhaler.

Adapted from Wolthers OD. Extra-fine particle inhaled corticosteroids, pharmacokinetics and systemic activity in children with asthma. *Pediatr Allergy Immunol*. 2016;27(1):13–21; Ciciliani AM, Wachtel H, Langguth P. Comparing Respimat Soft Mist Inhaler and DPI aerosol deposition by combined in vitro measurements and CFD simulations. Abstract presented at 2014 Respiratory Drug Delivery Conference, Fajardo, Puerto Rico.

When patients inhale a short-acting bronchodilator, they may inhale another dose shortly thereafter if they do not perceive a sufficient response from the first dose. By doing so, they can often overcome poor technique and potentially poor

disease control by increasing their dose. Patients do not get this feedback from controller inhaled therapies. For this reason, optimal particle size for the targeted site of deposition, optimal delivery system design, and technique of use may be more critical for achieving benefit from controller inhalers as compared with short-acting bronchodilators (25).

METERED-DOSE INHALERS

The pMDI is comprised of several components, including active drug, propellants/excipients, metering valve, actuator, and container (Fig. 37.3). Figure 37.4 shows a schematic diagram demonstrating the operation of a pMDI. Prior to actuation, the propellant–drug formulation for the subsequent single dose is contained within the small metering chamber inside the pMDI canister. During the actuation, the metering chamber briefly communicates with the atmosphere but is sealed off from the remainder of the formulation within the canister; at this time, the dose within the metering chamber exits the inhaler through the valve stem. Immediately after the dose is released, however, the valve blocks the connection of the metering chamber to the atmosphere but permits the chamber to communicate with the interior of the canister, allowing refilling of the metering chamber. Recommended inhalation technique with pMDI inhalers (used without additional spacer devices) is indicated in Table 37.3A.

Many studies have documented the prevalence of errors in patients' use of pMDIs (Table 37.4). Despite training, around 15% of individuals are not able to use inhalers properly without assistive devices. Of patients with initially inadequate technique who master proper technique with training, around 50% subsequently again develop significant deficiencies in technique over time (26).

Twenty-first-century pMDIs are less affected by many issues that were more significant for their CFC-propellant predecessors (27), including shaking (28) (not required at all for inhalers in which the drug is in solution rather than suspension in the propellant), cold Freon effect (29), priming of the inhaler after initial use (30), variability of dosing (31), and unreliability in cold weather (32). However, effective use of pMDIs still requires coordination of actuation with inhalation and a precisely executed inhalation technique which many patients find problematic. Adjunctive use of spacer devices with pMDIs was an initial approach—DPIs, breath-actuated pMDI inhalers, and the SoftMist Inhaler are other approaches which have emerged to address this issue.
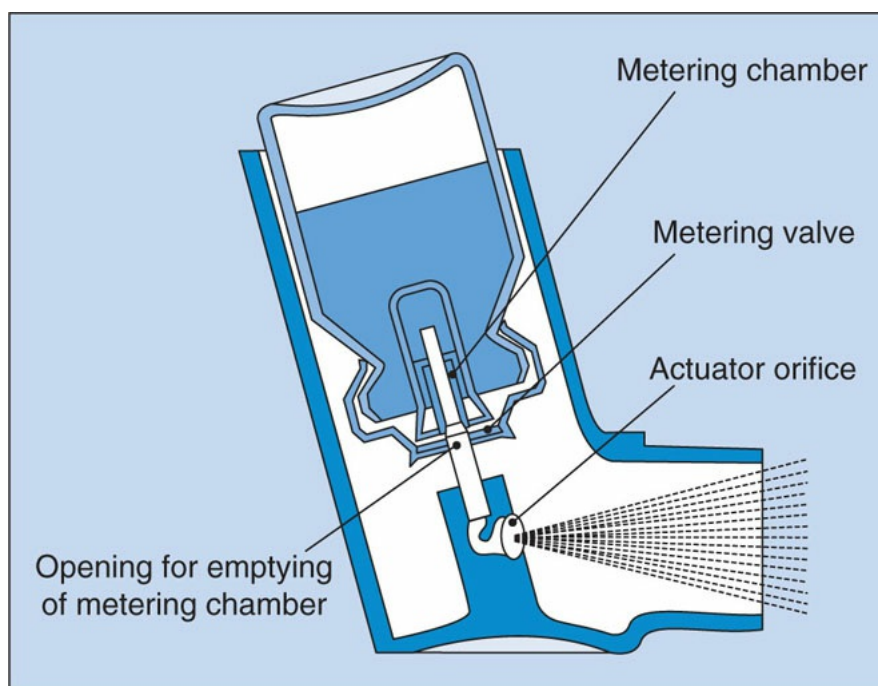
FIGURE 37.3 Schematic illustration of a typical pressurized metered-dose inhaler. (From Rees J. ABC of asthma-methods of delivering drugs. *BMJ*. 2005;331:504–506; with permission.)
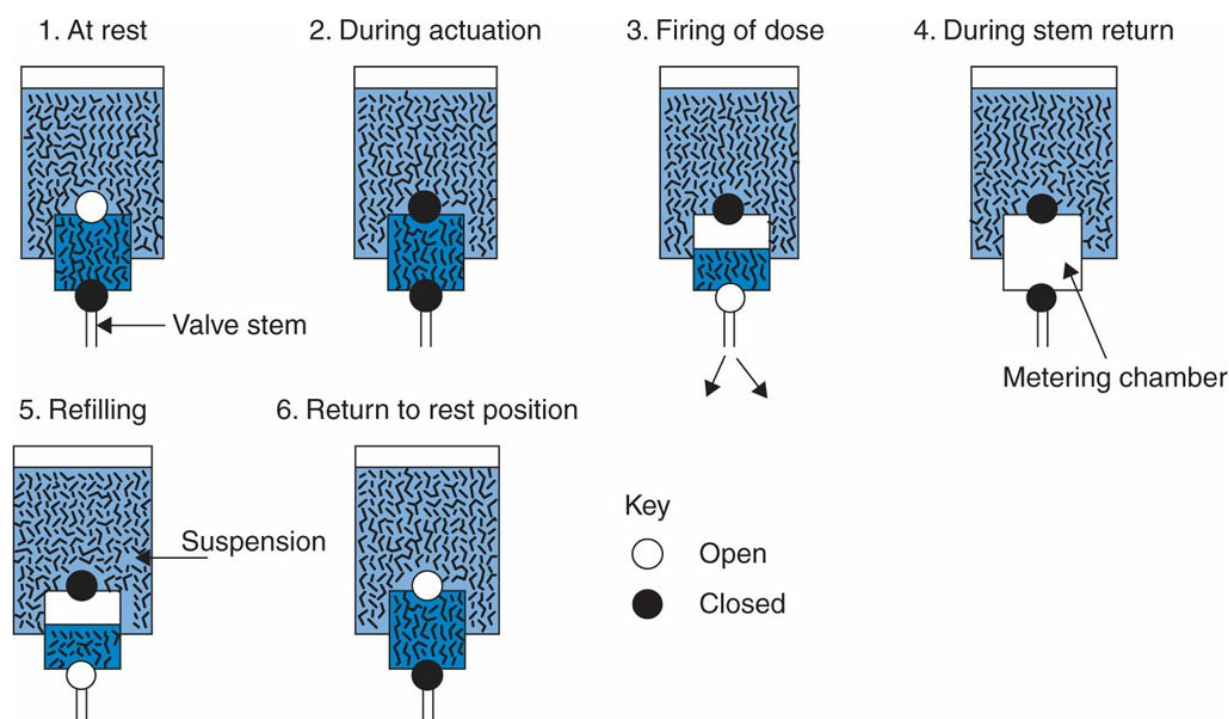
FIGURE 37.4 The operation of a propellant metered-dose inhaler valve. (Adapted from Purewal TS. Formulation of metered dose inhalers. In: Purewal TS, Grant DJW, eds. *Metered Dose Inhaler Technology*. Buffalo Grove, IL: Interpharm, 1998:9–68.)

TABLE 37.3 INSTRUCTIONS FOR USE OF PRESSURIZED

METERED-DOSE INHALER (PMDI), PMDI WITH HOLDING CHAMBERS (SPACERS), DRY POWDER INHALER (DPI), AND JET NEBULIZERS

A. pMDIS (WITHOUT SPACER): FOR PATIENTS WITH OBSERVED GOOD ACTUATION–INHALATION COORDINATION

1. Shake 4–5 times (unnecessary with solution formulations—Alvesco, QVAR, and Aerospan).

2. Take the cap off.

3. Prime the inhaler with initial use and if it has not been used in the previous 10–14 d (refer to Patient Information leaflet for specific instructions).

4. Exhale slowly, as far as comfortable (to empty the lungs).

5. Hold the inhaler in an upright position.

6. Immediately place the inhaler in the mouth between the teeth, with the tongue flat under the mouthpiece.

7. Ensure that the lips have formed a good seal with the mouthpiece.

8. Start to inhale slowly, through the mouth and at the same time press the canister to actuate a dose.

9. Maintain a slow and deep inhalation, through the mouth, until the lungs are full of air. This should take an adult 4–5 s.

10. At the end of the inhalation, take the inhaler out of the mouth and close the lips.

11. Continue to hold the breath for as long as possible, or up to 10 s before breathing out.

12. Breathe normally.

13.Repeat steps 4–12 for as many doses as are required.

B. pMDI + SPACER WITH FACE MASK: FOR PATIENTS ≤3 Y OLD OR ANYONE WHO CANNOT BREATHE CONSCIOUSLY THROUGH THE MOUTH

1–3. Same as above for pMDIs alone.

4. Insert the mouthpiece of the pMDI into the open end of the spacer and ensure a tight fit.

5. Place the face mask (appropriate size to fit patient's face) over the nose and mouth and be sure the fit is tight to the face.

6. Actuate one dose into the chamber of the spacer.

7. The patient should breathe (inhale and exhale) normally through the spacer for at least 10 breaths[a].

8. Take the face mask off the patient's face.

9. If another dose is required, repeat steps 1–8.

C. pMDI + SPACER WITH MOUTHPIECE: FOR PATIENTS >3 Y OLD (CLINICIAN AND CAREGIVER SHOULD DETERMINE WHETHER CHILD CAN PERFORM THIS TECHNIQUE CORRECTLY)

1–4. Same as above for spacer with face mask.

5.Place the mouthpiece of the spacer in the patient's mouth with the teeth over the mouthpiece and the lips sealed around it.

6.Actuate one dose into the chamber of the spacer.

7.The patient should breathe (inhale and exhale) normally through the spacer for at least 5 breaths[a].

8. If another dose is required, repeat steps 4–7.

D. pMDI + SPACER WITH MOUTHPIECE: FOR PATIENTS ≥6 Y OLD (CLINICIAN AND CAREGIVER SHOULD DETERMINE WHETHER A CHILD CAN PERFORM THIS TECHNIQUE CORRECTLY)

1–4. Same as above for spacer with face mask.

5. Place the mouthpiece of the spacer in the patient's mouth with the teeth over the mouthpiece and the lips sealed around it.

6. The patient should exhale slowly, as far as comfortable (to empty their lungs).

7. Actuate one dose into the chamber of the spacer and start to inhale slowly through the mouthpiece. Some spacers will make a whistling noise if inspiration is too fast.

8. Maintain a slow and deep inhalation through the mouth, until the lungs are full of air. This should take a child 2–3 s and an adult 5 s.

9. At the end of the inhalation, take the inhaler out of the mouth and close the lips.

10. Continue to hold the breath for as long as possible for up to 10 s before breathing out.

11. Breathe normally.

12. If another dose is required, repeat steps 1–11.

E. DPIs: FOR PATIENTS ≥ 5–6 Y OLD (CLINICIAN AND CAREGIVER SHOULD DETERMINE WHETHER A CHILD CAN PERFORM THIS TECHNIQUE CORRECTLY)

1. Take the cap off (some do not have a cap).

2. Follow the dose preparation instructions in the Patient Information leaflet.

3. Do not point the mouthpiece downwards once a dose has been prepared for inhalation because the dose could fall out.

4. Exhale slowly, as far as comfortable (to empty the lungs). Do not exhale into the DPI.

5. Start to inhale forcefully through the mouth from the very beginning. Do not gradually build up the speed of inhalation.

6. Continue inhaling until the lungs are full.

7. At the end of the inhalation, take the inhaler out of the mouth and close the lips. Continue to hold the breath for as long as possible, or up to 10 s.

8. Breathe normally.

9. If another dose is required, repeat steps 1–8.

F. JET NEBULIZERS: FOR PATIENTS OF ANY AGE WHO CANNOT USE A pMDI WITH A VALVED HOLDING CHAMBER, WITH OR WITHOUT A FACE MASK, OR IF THE DRUG IS ONLY AVAILABLE AS NEBULIZER LIQUID

1. Assemble the tubing, nebulizer cup, and mouthpiece (or mask).

2. Pour the medication solution into the nebulizer cup.

3. Do not exceed the fill volume recommended by the manufacturer.

4. Connect to power source; flow of 6–8 L/min, or compressor.

5. Place the mouthpiece in the mouth and close the lips around it (or cover the nose and mouth with an appropriate face mask).

6. Keep the nebulizer vertical during treatment.

| | 7. | Inhale and exhale using normal (tidal) breaths, with occasional deep breaths, until the nebulizer starts to sputter or no more aerosol is produced. |

8. If the treatment must be interrupted, turn off the unit to avoid waste.

9. At the completion of the treatment, take the mouthpiece out of the mouth.

10. Dismantle and clean nebulizer following the manufacturer's instructions.

11. With technology that differs from that of a traditional jet nebulizer, clinicians should thoroughly review operating instructions prior to patient use and instruction.

Rinse mouth after use of all preparations containing inhaled corticosteroids. Devices should be cleaned periodically according to instructions in the Patient Information leaflet.

[a]With some spacers, the inhalations and exhalations can be monitored by observing the movement of the valves or other components of the device.

Adapted from Laube BL, Janssens HM, de Jongh FH, et al. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J*. 2011;37:1308–1331.

TABLE 37.4 ERRORS IN PATIENT USE OF METERED-DOSE INHALER (MDI)

	% OF PATIENTS
Breath-hold too short	44
Excessively rapid inspiratory flow rate	34
Incomplete inhalation	23
Device not actuated at the beginning of inhalation	19
Multiple actuations with one inhalation	19

Actuation at the end of inhalation	18
Nasal inhalation after actuating MDI into mouth	12
Wrong position of inhaler	7
No inhalation	6
Failure to remove cap	0.4

Adapted from Giraud V, Roche N. Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability. *Eur Respir J*. 2002;19:246–251.

SPACER DEVICES: ADJUNCTS TO METERED-DOSE INHALERS

Spacer devices are inhalation aids designed for use with pMDIs to overcome coordination difficulties, enhance aerosol deposition in the lower airways, and minimize oropharyngeal deposition (Fig. 37.5). Reduction in oropharyngeal deposition occurs in all patients while improvement in lung deposition is an effect primarily significant in patients with poor pMDI technique or during exacerbations. Although many types of spacer devices are available, the spacer devices most commonly utilized currently are 120 to 200 mL valved holding chambers. Larger sized chambers used more frequently in the past provide no advantage over smaller devices when used with current HFA propellant inhalers (33). These holding chambers remove virtually all particles greater than 5 µm in size (33). A mouthpiece attachment with standard inhalation technique for pMDIs is utilized for older children and adults who can control their respiration (Table 37.3D); tidal respiration through a valved holding chamber with mouthpiece may be appropriate for some younger children who can seal their lips around the mouthpiece but who cannot fully control their respiration. A face mask attachment and tidal respiration is utilized in other situations (Table 37.3B). It has been shown *in vitro* that even a small air leak in the face mask can dramatically reduce the efficiency of drug delivery; lung dose was higher with leaks near the chin than for leaks near the nose (34,35). Aerosolized drug delivery with face mask may increase facial and eye deposition of aerosol with potential for local adverse effects. However, actual occurrence of such effects

has been minimal in children (36). Delivery of drug by mouthpiece is more efficient than by face mask; patients should be transitioned to mouthpiece as early as possible (37). A proportion of drug particles emitted by a pMDI carries an electrostatic charge. Static electricity accumulates on some plastic spacer devices, which may attract and bind these drug particles on the device's surface, thus producing variability in the dose of drug delivered; prewashing with detergent was proposed to deal with this issue (38). Metal chambers and most current plastic chambers manufactured with antistatic materials may be used out of the package without prewashing (39). Holding chambers should be cleaned and eventually replaced periodically in accordance with the manufacturers' recommendations and labeling.
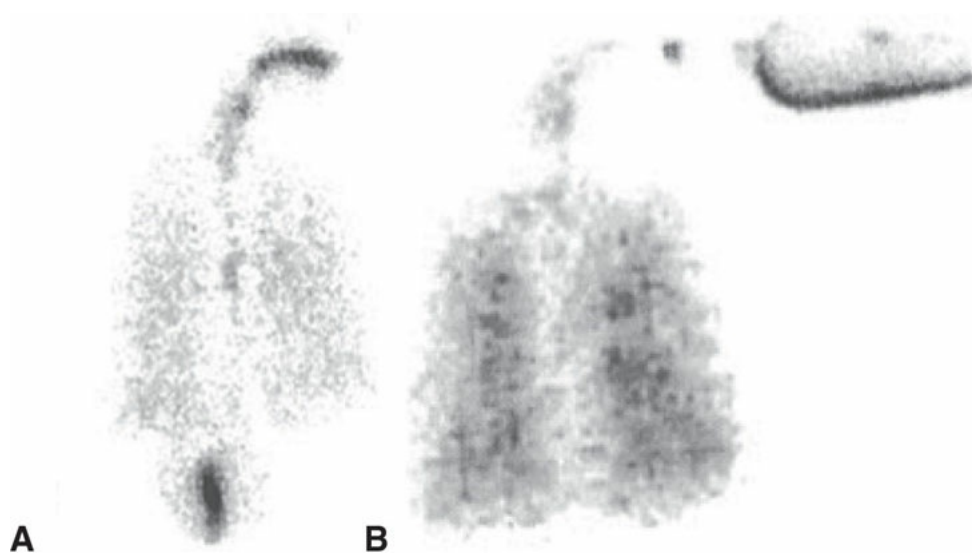
■ **FIGURE 37.5** Scintigraphic images obtained utilizing radiolabeled flunisolide; spacer used with pressurized metered-dose inhaler (MDI) results in increased pulmonary delivery of aerosol with reduced oropharyngeal and gastric (swallowed drug) deposition; capture of aerosol particles on the walls of the spacer is noted. Images were obtained from the same subject on different days. Pressurized MDI alone **(A)** and MDI with 250 mL tube spacer **(B)**. (Adapted from Newman SP, Steed KP, Reader SJ, et al. Efficient delivery to the lungs of flunisolide aerosol from a new hand-held portable multidose nebulizer. *J Pharm Sci*. 1996;85:960–964.)

It was recognized shortly after introduction of spacers into clinical practice that, as a result of reduced oropharyngeal deposition (Fig. 37.5), local adverse effects of candidiasis and hoarseness from inhaled corticosteroids are minimized significantly (40). When moderate or high dosages of inhaled corticosteroids are administered via pMDI, it is usual practice to routinely prescribe a spacer device. As compared to use of pMDI without spacer, systemic bioavailability of

fluticasone (minimal GI bioavailability) increased as a result of increased pulmonary deposition with use of the spacer (41), whereas systemic bioavailability of beclomethasone (absorbed from the GI tract in contrast to fluticasone) is diminished with spacer use because the reduction in swallowed drug resulting from decreased oropharyngeal deposition overshadows the effect of increased pulmonary deposition (42,43). Because of these considerations, results of clinical trials defining safety and efficacy of an inhaled medication formulation used without spacer devices cannot necessarily be generalized to use of the same formulation when used in conjunction with a spacer device.

Routine use of spacers in accordance with Table 37.3 instructions is recommended in the following clinical scenarios:

- Children ≤6 years of age using pMDIs (44);

- pMDIs are used during acute asthma exacerbations (45);

- When moderate or high doses of inhaled corticosteroids are administered via pMDI (downward dosage adjustment may be need to be considered and may be facilitated), and in those patients utilizing lower dosages of inhaled corticosteroids who develop hoarseness, candidiasis, or other oropharyngeal adverse effects (40).

- Patients using pMDIs who have not been documented to show excellent inhaler coordination technique, including many adult patients (25).

Despite the demonstrated benefits, simplicity, and low cost of spacers, use of these devices transforms the pMDI into a more bulky device which is difficult to transport and use discreetly, and is the inhalation method least preferred by patients (46).

Considerations for pMDI/Spacer Device Use in Infants and Young Children

The use of valved holding chambers with mask to deliver medications to infants and toddlers via tidal breathing differs considerably from the considerations that apply to the usual administration to older children and adults. Based on radionuclide studies conducted by Tal et al, in this situation, only around 2% of the dose placed into the holding chamber is deposited into the patient's lungs, a roughly 10-fold reduction from what is typically observed in older patients (47). However, if the patient is crying during the administration of the aerosol, lung deposition of less than 0.35% was observed. Ideally inhalation should be administered when the patient is calm or asleep. The mask should remain sealed

over the patient's face for 20 to 30 seconds of tidal breathing after actuation of the MDI. Tal et al. (using a plastic spacer without special precautions to reduce electrostatic charge) found longer periods of time to be useless because the aerosol adhered to the spacer after 30 seconds. Because of the expected 10-fold reduction in pulmonary deposition, the full adult dose of aerosol medication, typically at least two puffs, is administered (47). It may be appropriate to start with several puffs, a dose larger than would be typically used in older children and adults, then to reduce the dose once it is clear that the treatment is effective (48). The SootherMask is a novel approach which can deliver inhaled medication to sleeping infants. The nipple of the infant's pacifier is inserted through a slot in the anterior wall of the mask. The infant, sucking on the pacifier mask, keeps the mask sealed to its face by means of subatmospheric pressure, and can nasally inhale the medication generated from an pMDI plus valved holding chamber attached to the pacifier mask (49).

BREATH-ACTUATED METERED-DOSE INHALERS

The breath-actuated devices are alternatives to holding chambers developed to improve coordination of actuation of conventional pMDIs with inhalation. These devices are designed to actuate the MDI automatically with a spring mechanism as the patient inhales. Although these devices are of little additional benefit to patients with good inhaler coordination, use of a breath-actuated inhaler in those with poor coordination increased the deposition of radiolabeled CFC bronchodilator aerosol into the lungs from a mean of 7.2% with a conventional MDI to a mean of 20.8% with a breath-actuated inhaler; there was a corresponding dramatic improvement in FEV_1 after breath-actuated inhaler use as compared with that measured after conventional pMDI in these patients (50).

Dependence on inspiratory flow is a theoretical drawback of the breath-actuated inhaler. At least one case has been described in which a patient experiencing acute severe airway obstruction was not able to generate sufficient inspiratory flow to activate the device (51), suggesting that, in rare instances, this issue may be clinically significant, especially when rescue bronchodilators are incorporated into breath-actuated inhalers.

DRY POWDER INHALERS

An alternative to the pMDI (used alone or in conjunction with spacer or breath-actuated devices) is the DPI. In general, DPIs are easier to use effectively than MDIs because they are inherently breath actuated. The current routinely available DPIs require an inspiratory flow rate of at least 60 L/minute for

optimal dispersion of the powdered medication into respirable particles (52); below 30 L/minute, the fine particle output may be reduced by as much as 50% (53). Consequently, concerns have been raised regarding possible inadequacy of drug delivery to the airways from DPIs during severe exacerbations; however, studies of DPI-delivered β-agonists in acute worsening of asthma in older children and adults have not borne out such concerns (54). Because of inspiratory flow dependency, small children as well as adults with cognitive impairment may not be able to use DPIs effectively. In one study, only 40% of preschool children with acute wheezing could generate an inspiratory flow rate exceeding 28 L/minute, although around 75% could exceed this inspiratory flow rate during periods of stable asthma (55).

Overall pulmonary deposition from DPIs is similar to that of a suspension formulation (non–extra-fine particle) pMDI with spacer; fine particle mass is around 20% with the available DPIs at the usual inspiratory flow rates (52,53). Hoarseness and other undesirable oropharyngeal effects are common with high-dose inhaled corticosteroid preparations delivered via DPI but typically are not problematic with low-dose inhaled corticosteroids administered in this way.

Currently available DPIs may be categorized into the following three groups.

1. *Single-dose DPI*: In a single-dose device, each dose is loaded into the device before use. The drug is supplied in an individual single-dose capsule which is placed into the inhaler and is pierced by spears or severed by a twisting action; the powder is then inhaled by the patient. After use, the remains of the capsule are removed. The Aerolizer device supplied with formoterol (Schering Corporation) and the HandiHaler device supplied with tiotropium (Boehringer Ingelheim Pharmaceuticals, Inc.) are single-dose DPIs.

2. *Multiple-dose reservoir DPI*: The first such inhaler to be developed was the Turbuhaler (Fig. 37.6), still utilized in many parts of the world but now replaced in the United States by a similar device, the Flexhaler (AstraZeneca). It contains a bulk supply of powdered drug without a carrier from which individual doses are released with each actuation. The Pressair (known as Genuair in several other countries) (AstraZeneca) is a novel multiple-dose reservoir device (56) currently available in the United States for delivery of aclidinium bromide, a long-acting muscarinic antagonist agent labeled for treatment of chronic obstructive pulmonary disease. The Respiclick inhaler, marketed in the United States by Teva as a delivery device for albuterol, is similar to the Spiromax inhaler (Fig. 37.7) used in Europe. It is a multiple-dose reservoir DPI that utilizes an air pump to transfer drug powder from the

reservoir to the dosing cup when the cap is opened, a cyclone technology to deagglomerate the drug particles from the lactose carrier prior to inhalation, and is designed to externally resemble a conventional pMDI (57). Patients should be reminded that the inhalation technique to be used with the Respiclick is the rapid forceful inhalation appropriate for a DPI.
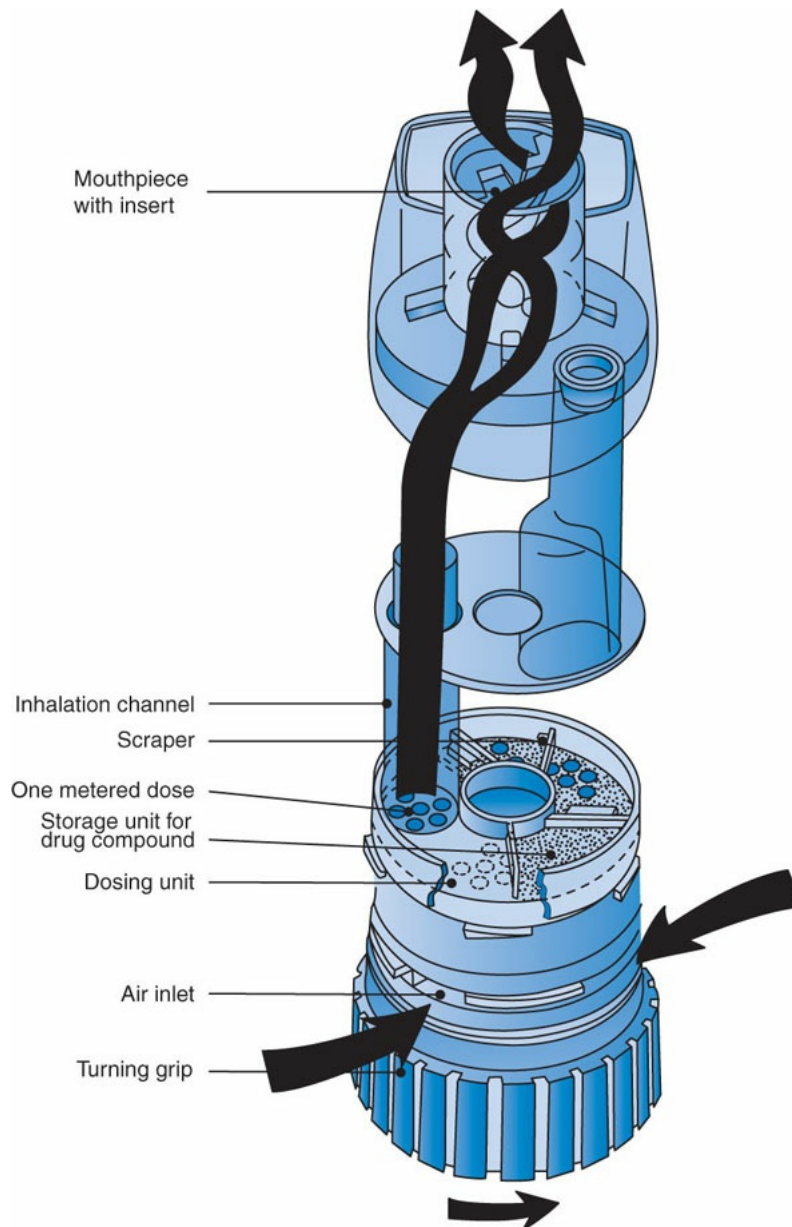
■ **FIGURE 37.6** Turbuhaler is a cylindrical, multiple-dose reservoir dry powder inhaler device. Dosing is achieved by twisting the turning grip back and forth followed by deep inhalation. (From Vaswani SK, Creticos PS. Metered dose inhaler: past, present, and future. *Ann Allergy Asthma Immunol.* 1998;80:11–21; with permission.)

3. *Multiple unit-dose DPI*: These devices utilize individually prepared and sealed doses of drug. The Diskus device shown in Fig. 37.8 contains a coiled

strip of 60 double foil-wrapped individual doses. The patient operates the inhaler by sliding a lever which moves the next dose containing blister into place with simultaneous peeling apart of two layers of foil, exposing the dose ready for inhalation (58). The more recently developed Ellipta device also utilizes coiled strips of individual doses. For a combination therapy Ellipta product, the inhaler is supplied in the two-strip configuration with two 30-dose blisters that contain separate drug formulations (Fig. 37.9); one blister from each strip is delivered simultaneously during a single inhalation to provide a single dose of the combination therapy (59).
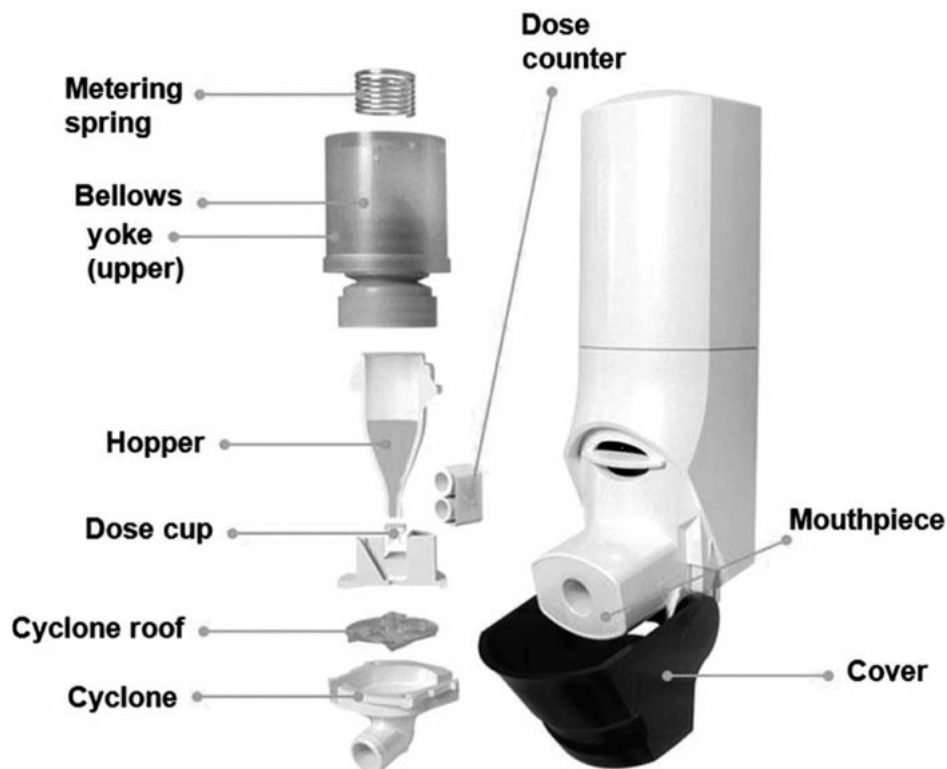
■ **FIGURE 37.7** Configuration of the Spiromax multidose dry powder inhaler, externally resembling a metered-dose inhaler.
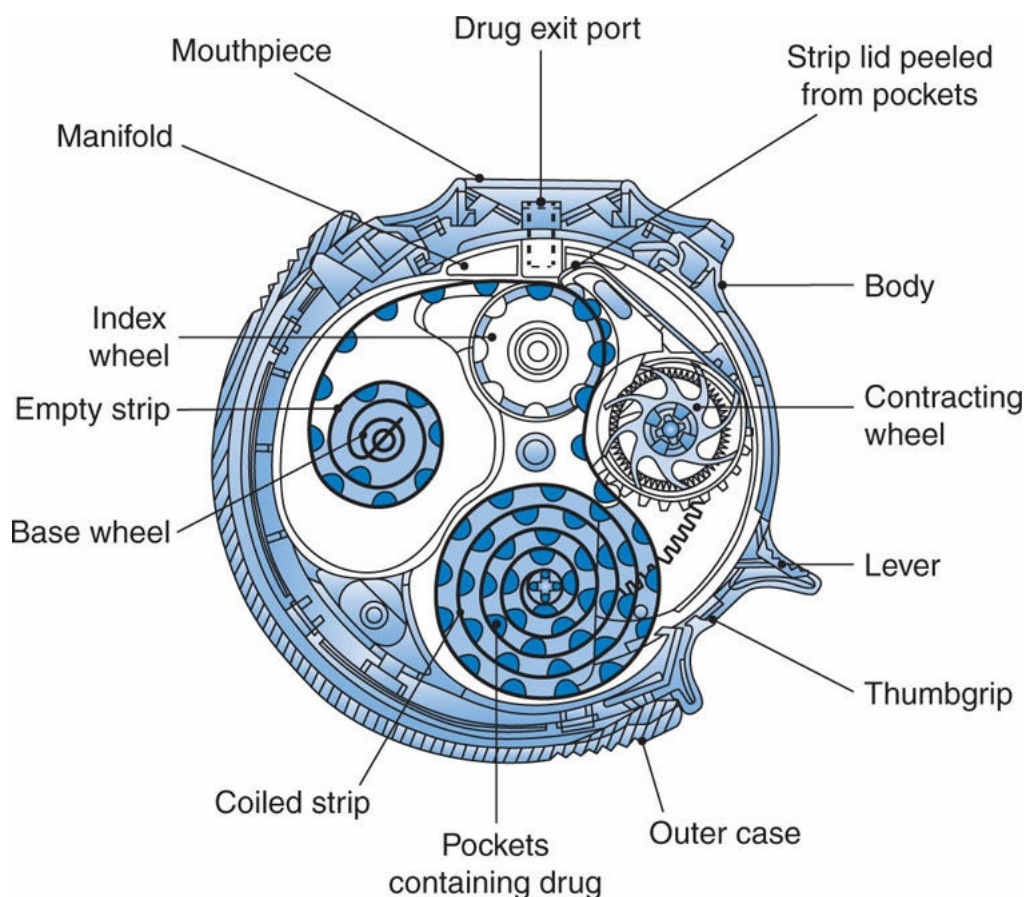
FIGURE 37.8 Diskus is a disk-shaped, pocket-size, multiple unit-dose dry powder inhaler device. During inhalation, air is drawn through the device delivering the dose via the mouthpiece. It contains 60 metered doses and has a built-in dosage counter. (From Vaswani SK, Creticos PS. Metered dose inhaler: past, present, and future. *Ann Allergy Asthma Immunol*. 1998;80:11–21; with permission.)

General instructions for use of DPIs are provided in Table 37.3.

Electronic DPIs incorporating features such as dose delivery confirmation, adherence monitoring, and dosing reminders into portable inhalers are under active investigation (60,61). Although DPIs are believed to be less likely to be misused than pMDIs, serious errors remain frequent and significant. Westerik reported that 55% of patients made ≥1 serious error with a multi-use DPI. The most common errors were the failure to exhale before inhalation, insufficient breath-hold at the end of inhalation, and inhalation that was not forceful from the start; these errors correlated with adverse outcomes, including asthma hospitalization and poor asthma control, and correlated with no inhaler technique review within the past year (62). Error rates exceeding 80% in use of routinely available DPIs have been documented in elderly patients with severe airway obstruction who have not received any training in use of these devices (63).

SOFT MIST INHALER

The Respimat Soft Mist Inhaler (SMI) (Fig. 37.10), a device similar in size to a pMDI, utilizes a unique method of generating aerosolized droplets. A 15-µL aliquot of drug formulation solution is forced through a two-channel filter/nozzle glass and silicon system (the "uniblock"), causing it to be accelerated and split into two converging jets which collide at a carefully controlled angle; this results in the drug solution's disintegration into inhalable droplets (12). Before each actuation, the patient tensions the spring by twisting the device at 180°. The fine particle fraction for most formulations is around 75%, significantly higher than DPIs and pMDI aerosols. The velocity of the aerosol cloud is 3 to 10 times slower than the speed of release from a pMDI. The lower velocity is expected to reduce oropharyngeal deposition and increase the fraction of the emitted dose which reaches the airways (12). The spray duration of the Respimat SMI is 1.2 seconds, significantly longer than 0.15 to 0.36 second spray duration of pMDI mists (64). The long spray duration of the soft mist allows the patient a better chance of coordinating the inhalation maneuver with drug release. In one study, the mean lung deposition of a drug formulation delivered via SMI was 37% of the emitted dose in untrained subjects and 53% in subject who received training, versus 21% for both trained and untrained subjects with a pMDI HFA suspension formulation (12). Scintigraphic imaging generally has demonstrated relatively uniform pulmonary deposition of aerosols generated by the SMI (Fig. 37.11). The major shortcoming of the SMI is the currently limited number of drug formulations available with this device.
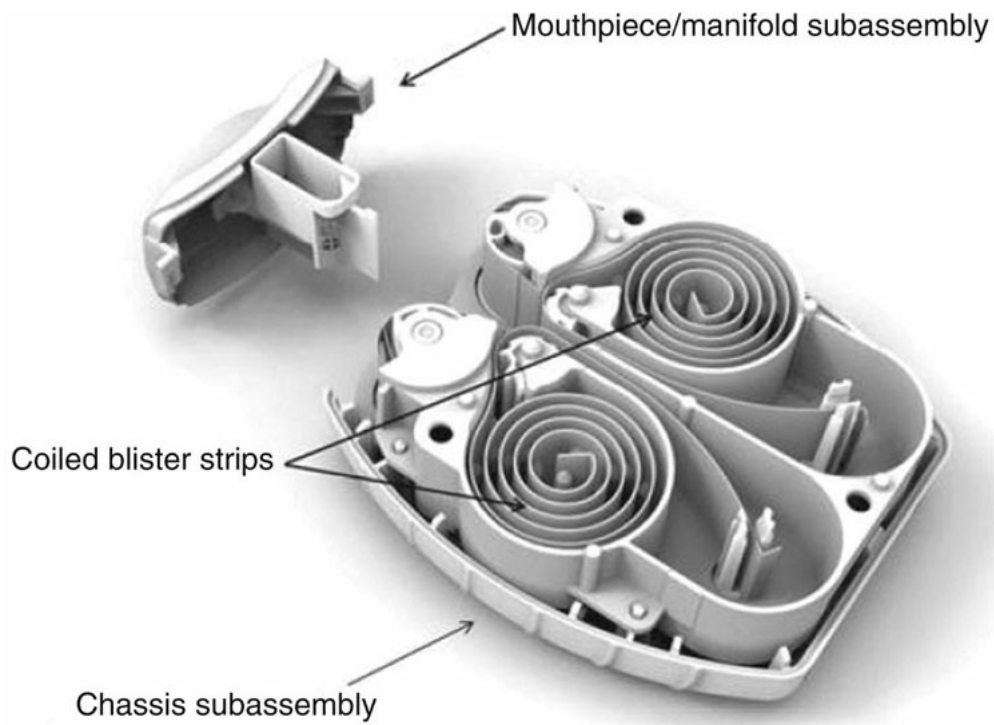
■ **FIGURE 37.9** View of coiled blister strips within the inhaler chassis and mouthpiece/manifold assembly of the Ellipta inhaler.
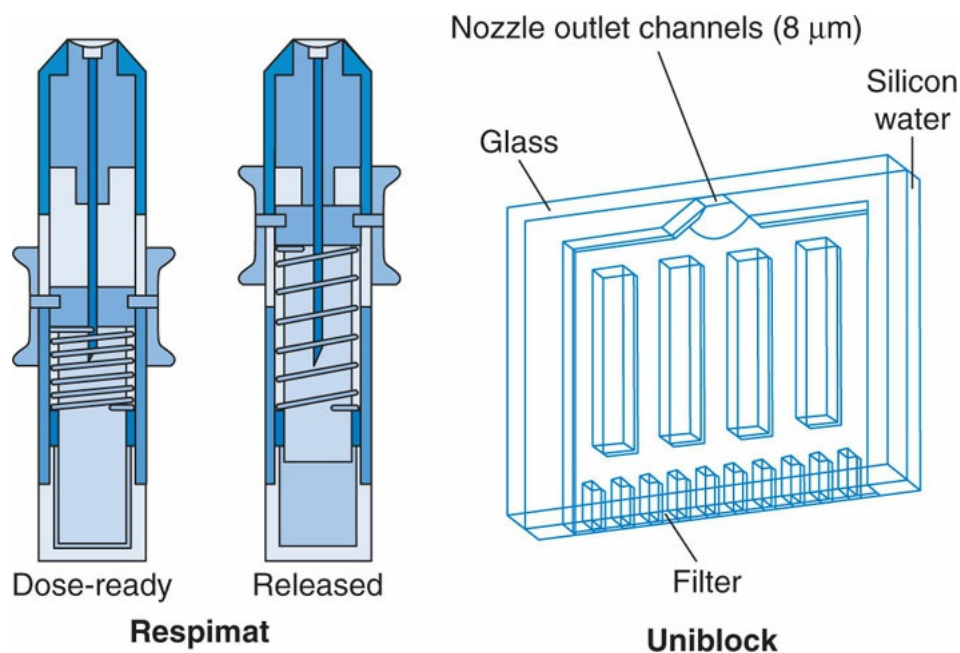
■ **FIGURE 37.10** Schematic illustration of the spring-powered Respimat (Boehringer Ingelheim) inhaler with "uniblock" designed to emit aerosols with enhanced pulmonary deposition. (From Dennis JR, Nerbrink O. New nebulizer technology. In: Bisgaard H, O'Callaghan C, Smaldone G. *Drug Delivery to the Lung.* New York, NY: Marcel Dekker, 2001:320; with permission.)

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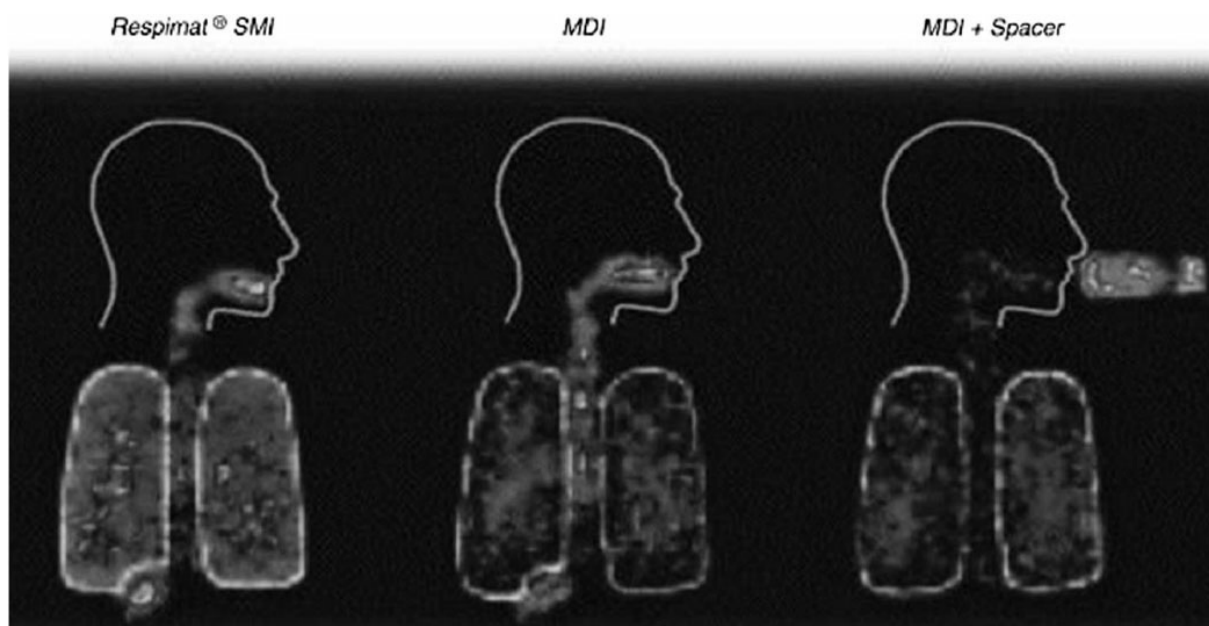
■ **FIGURE 37.11** Scintigraphic scans from one individual showing the deposition of radiolabeled aerosol in the lungs immediately after administration of a single dose of 250 μg flunisolide delivered via Respimat inhaler, pressurized metered-dose inhaler (MDI) or pressurized MDI plus spacer, on each of three study days. (From Dalby R, Spallek M, Voshaar T. A review of the development of Respimat SoftMist Inhaler. *Int J Pharm*. 2004;283:1–9; with permission).

■ CONCURRENT USE OF DPI AND PMDI INHALERS

The slow and deep inhalation technique optimal with pMDIs differs from the forceful and fast technique which is advantageous with DPIs. It has been demonstrated that patients make fewer errors (65,66) with improvement of asthma control and significant reduction in exacerbations (67) when exclusively utilizing one type of inhaler in contrast to mixing of the pMDI and DPI devices. Therefore, whenever possible, the inhalers prescribed for a patient's concurrent use should be of the same type (25,68). Congruity of rescue inhaler with DPI controller inhalers has recently become possible for many patients in the Unites States with the recent launch of a DPI albuterol inhaler labeled for use in older children and adults. Another undesirable occurrence is therapeutic substitution of one inhaler for another of a different type without patient instruction and assessment of proficiency with the newly introduced type of inhaler (69). Because the inhalation technique used with the SMI is similar to that used with pMDIs, the concurrent use of these devices would not be expected to be problematic; however, this issue has not been specifically investigated.

■ NEBULIZERS

A device that simply sprays gas through a liquid resulting in aerosolization is termed an *atomizer*. In contrast, nebulizers are more complex devices which, by the incorporation of baffles, selectively remove particles that are too large to enter the lower airways. Many types of nebulizers are available for various applications (25,27). Nebulizers most commonly used in aerosol drug therapy are jet nebulizers driven by air compressors. In the jet nebulizer, the compressed air moves through a narrow hole known as a venturi. Negative pressure pulls liquid up to the venturi by the Bernoulli effect; at the venturi, the liquid is subsequently atomized. Many of the droplets initially atomized are much larger than the 5-μm maximum necessary for them to enter the smaller lower airways. These large particles impact on the nebulizer's baffles or the internal wall of the nebulizer and return to the reservoir for renebulization. Details of the baffle design have a major effect on the sizes of the particles produced.

The traditional jet nebulizer design (Fig. 37.12) most commonly used provides continuous flow of gas from the compressor into the nebulizer; the rate of aerosol outflow from the nebulizer is equal to the inflow rate from the compressor and does not change with the phases of respiration. Typically, only 7% to 25% of medication placed into the nebulizer is delivered to the patient's airway (70,71). For drugs that are relatively inexpensive and have a high therapeutic index such as bronchodilators, it is simple and effective to compensate for this loss by placing a large dose of medication into the nebulizer; provided that the dosage delivered to the patient is within the flat range of the dose–response curve, the precision and efficiency of delivery may not be a critical issue. However, these factors may become meaningful when medications that are expensive and/or have a greater potential for significant dose-dependent adverse effects, such as corticosteroids, are used. Breath-assisted open vent nebulizers are a modification in which the vent is designed to be open only during inspiration, enhancing aerosol generation only during the inspiratory phase. Aerosol generation continues as a result of the continuous gas flow from the compressor during expiration, but is not enhanced by the vent, which is closed during expiration (Fig. 37.13). The primary advantages of this nebulizer design include significantly improved delivery of the drug placed into the nebulizer into the airway and shorter time required for its nebulization; other benefits include the generation of a greater fraction of smaller particles caused by increased evaporation from droplets owing to the additional airflow, and the need for less powerful compressors (70). General instructions for use of jet nebulizers are provided in Table 37.3F.

For a single drug preparation, various nebulizers may provide widely

differing drug delivery that further varies depending on the patient's tidal volume during nebulization. In models of nebulization of budesonide suspension, using various nebulizer devices and tidal volumes ranging from 75 to 600 mL, the estimated percentage of the dosage placed into the nebulizer that is inhaled varied over a wide range depending on these factors (71).
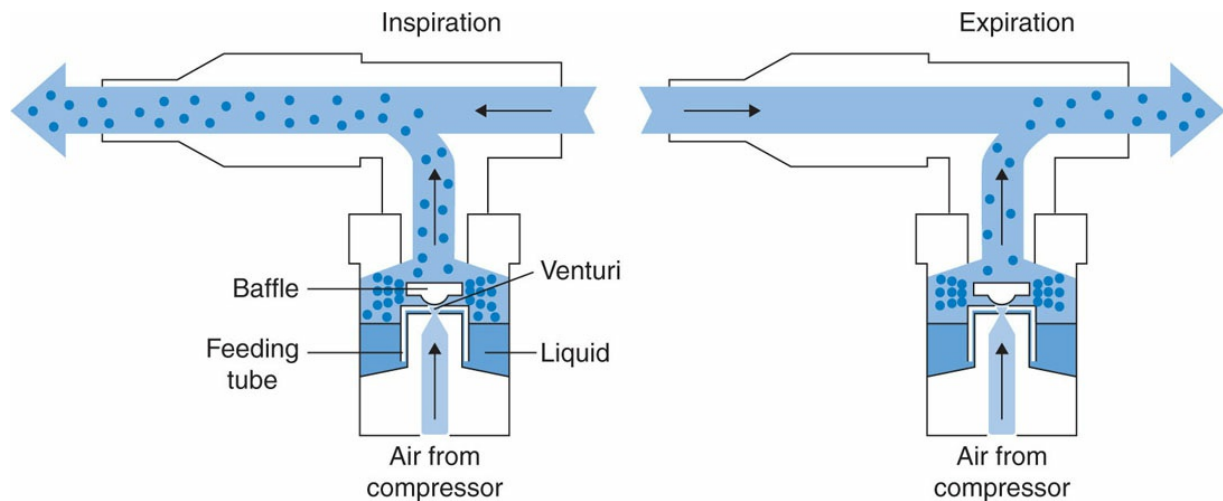
■ **FIGURE 37.12** Conventional nebulizer design. Air from the compressor passes through a small hole (venturi). Rapid expansion of air causes a negative pressure, which sucks fluid up the feeding tube system, where it is atomized. Larger particles impact on baffles and the walls of the chamber and are returned for renebulization. Small aerosol particles are released continuously from the nebulizer chamber. On expiration, the nebulizer continues to generate aerosol, which is wasted. (From O'Callaghan C, Barry PW. The science of nebulized drug delivery. *Thorax*. 1997;52[Suppl 2]:31–44; with permission.)
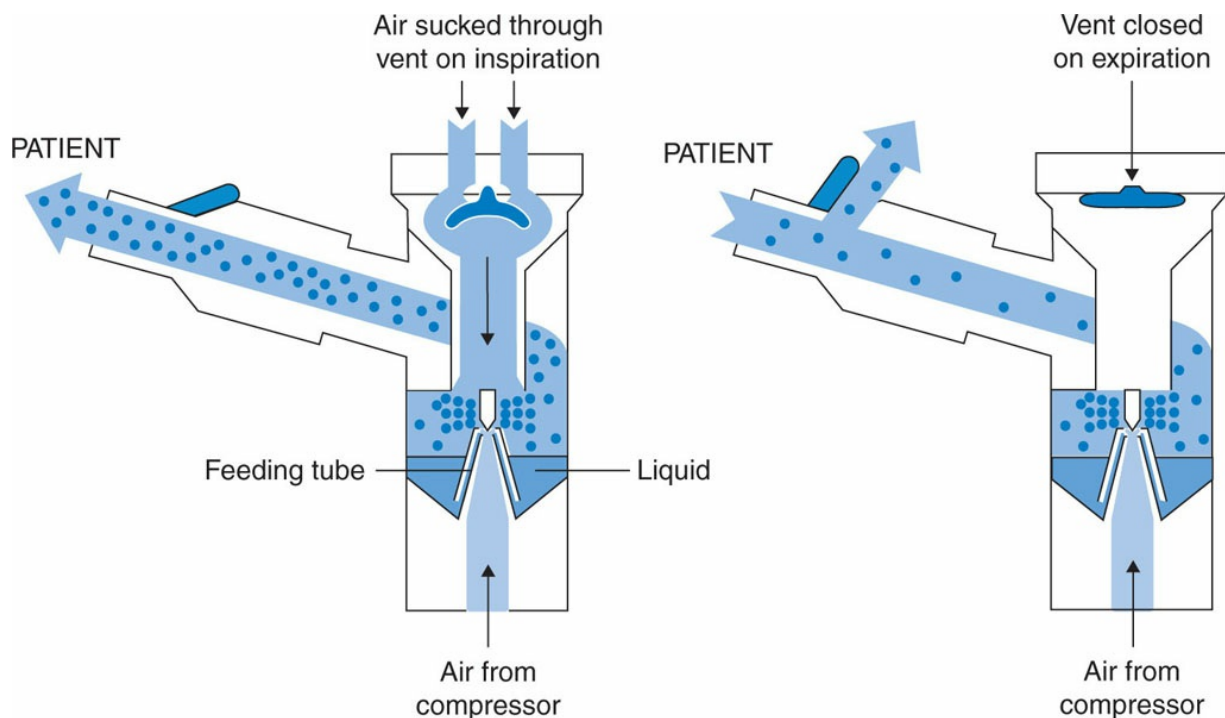
■ **FIGURE 37.13** An example of an open vent nebulizer, the Pari LC Jet Plus. On inspiration, the valve located at the top of the chamber opens, allowing extra air to be sucked through the vent. The main effect of this is to pull more aerosol from the nebulizer on inspiration, increasing the dose to the patient. On expiration, the vent closes, and aerosol exits via a one-way valve near the mouthpiece. Aerosol lost from the nebulizer on expiration is thus proportionally less than that from a conventional nebulizer. Nebulization times will be faster, and the drug dose received by the patient will be significantly greater than with conventional nebulizers. (From O'Callaghan C, Barry PW. The science of nebulized drug delivery. *Thorax*. 1997;52[Suppl 2]: 31–44; with permission.)

Effective drug delivery to the airways of infants and toddlers depends on proper nebulization techniques and minimization of crying. A point of controversy is the effectiveness of aerosolized medications delivered by hood or "blow-by" from a mask or extension tubing held in front of the patient's face (instead of delivery using a tightly fitting face mask, to which young patients often object). While some studies have suggested that the blow-by approach may provide acceptable drug delivery when a high-performance nebulizer system is used (72,73), others have concluded that blow-by generally provides only negligible pulmonary drug delivery (74); therefore, use of the blow-by method is generally discouraged (75). Aerosol therapy delivered to wheezing infants with a hood interface (76–78) may be a better alternative than blow-by for delivering inhaled medications via nebulizer to young children who cannot tolerate face mask treatment (75). The pacifier mask mentioned earlier in this chapter for use

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with MDI and face mask may also be utilized effectively in infants as a nebulizer interface and is being investigated as an interface with the Respimat SMI device (49). Drug delivery via valved holding chambers with mask is generally preferred to nebulizers in toddlers (79) because of shorter treatment times. Some toddlers and their caregivers object to the facial pressure needed to provide a tight seal for effective use of a valved holding chamber and instead prefer the lighter pressure of the nebulizer face mask.

When instructed that incremental doses of up to 10 puffs of pMDI β-agonist rescue inhaler via spacer may be used for acute asthma episodes, older children and adults usually prefer this approach to nebulizer therapy for acute asthma (25). A home nebulizer may be the best option for some elderly patients with limited manual dexterity (25). Nebulizers are utilized for continuous delivery of β-agonists in hospitalized patients with life-threatening asthma. General age and medication-specific recommendations for choice of aerosol delivery devices are shown in Table 37.5.

Most drugs used for nebulization currently are supplied in single-use ampoules, largely eliminating the need for preservative additives, some of which have been documented to have significant bronchoconstrictor effects. When multiple-use vials are used, the clinician should be aware of the additives present and any bronchoconstrictor potential that these may have with repetitive dosing (80).

TABLE 37.5 USUAL RECOMMENDATIONS FOR USE OF AEROSOL DELIVERY DEVICES (UNITED STATES)

AGE (y)	FIRST CHOICE(S)	SECOND CHOICE
0–3	MDI with spacer and face mask (pacifier mask preferred in infants)	Nebulizer
3–6	MDI with spacer	Nebulizer
6–12 (bronchodilators)	MDI with spacer	
>12 (bronchodilators)	MDI with spacer	MDI alone[a]

>6 (low-dose ICS with or without LABA)	DPI or MDI with spacer	
>6 (high-dose ICS with or without LABA)	MDI with spacer	DPI
Acute bronchial obstruction (all ages)	MDI with spacer	Nebulizer
Continuous bronchodilator therapy prescribed in emergency department, intensive care unit (all ages)	Nebulizer	

Soft Mist Inhaler is a first choice when available for a clinically indicated drug formulation.

[a]Only for those patients who demonstrate excellent technique with MDI alone.

DPI, dry powder inhaler; ICS, inhaled corticosteroids; LABA, long-acting β antagonist; MDI, metered-dose inhaler.

CONCLUSION

Published evidence shows that, *when used correctly*, there is little difference in clinical efficacy between different inhaler types (81). Despite the development of several new and improved types of inhaler devices over the past 60 years described above, there has been no sustained improvement in patients' ability to use their inhalers (27). In real-life studies, a large percentage of patients have shown serious deficiencies in their inhaler technique (82), and a majority of physician care providers are not able to provide sufficient instruction to their patients (83). Inadequate inhaler technique has clinical and economic consequences—in a cross-sectional study involving over 1,600 asthma outpatients, the finding of a single critical error in inhalation technique, irrespective of use of a pMDI or DPI, was associated with increased emergency department visits, hospitalizations, and oral medication utilization for asthma (84). As discussed earlier, outcomes are improved with avoidance of concurrent use of different types of inhalers in individual patients (67,85) and avoidance of switching of devices without personalized instruction (69). Provision of written materials does not substitute for direct observation, assessment, and instruction in technique appropriate for inhalers prescribed (86). At best, inhaler technique does not receive the prominence it deserves from patients, caregivers, care providers, and health insurance administrators; this situation clearly results in a major degree of modifiable morbidity and expense (27,87). All clinicians and

organizations involved in asthma management must recognize the incontrovertible imperative for increased emphasis, advocacy, and funding in this vital element of asthma care.

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Novel Immunologic Therapies, Including Biologics

LESLIE C. GRAMMER

NOVEL IMMUNOLOGIC THERAPIES

Afflicting up to 20% of the American population, allergic diseases are very prevalent; novel immunologic approaches to their abatement are avidly pursued. These approaches generally can be divided into four strategies. One approach is to administer monoclonal antibodies against molecules, usually proteins, that have been reported to be key in mediating allergic inflammation. Another is to administer other monoclonal proteins that will interfere with the allergic inflammatory process. A third approach is to target new enzymes or receptors with traditional low-molecular-weight (LMW) pharmacologic agents. A final strategy is to modify allergen immunotherapy using innovative techniques to reduce allergenicity and maintain and/or enhance immunogenicity; the latter is discussed in Chapter 13.

PHENOTYPES AND ENDOTYPES

While some diseases that allergists treat are fairly homogeneous, many are not. Allergic rhinitis is an example of a fairly homogeneous disease that varies in severity but not in underlying mechanisms involved (1). Asthma, on the other hand, is a very heterogeneous disease. Several phenotypes (observable characteristics) have been described; they include severe nonatopic asthma with frequent exacerbations as well as early-onset mild allergic asthma. These different phenotypes are thought to have disparate underlying mechanisms and, therefore, are likely to respond to different novel therapies, depending upon the target of that therapy. This has led to the concept of endotype, that is, a group of individuals whose disease, in this case asthma, is caused by distinct pathophysiologic or biologic underlying mechanisms (1). For example, individuals whose asthma is primarily allergic would be more likely to respond to an anti-immunoglobulin E (IgE) therapy than to an anti-interleukin (IL)-17 therapy. If an individual with asthma is nonatopic and has high levels of IL-17

and neutrophils in the sputum, then that individual might respond to anti-IL-17 therapy but would be less likely to respond to anti-IgE therapy. In short, these novel therapies are starting to assist in defining endotypes of allergic and related diseases. Table 38.1 lists target molecules, drugs, mechanisms, and diseases in which each novel therapy has been evaluated.

■ MONOCLONAL ANTIBODIES

Monoclonal Anti-immunoglobulin E

The elimination of IgE to provide an effective therapy for allergic diseases is based on the importance of IgE in both early- and late-phase reactions (2). Various strategies have been used to interfere with the binding of IgE to its receptors, thus abrogating allergic disease. Examples include inhibiting IgE production, use of IgE fragments to occupy the receptor, administration of soluble receptors to bind free IgE, and neutralizing antibodies against IgE. Polyclonal and monoclonal anti-IgE antibodies have been produced to study mechanisms of allergic disease (2). Omalizumab is a recombinant humanized monoclonal antibody that is reported to be effective for the treatment of patients with moderate-to-severe persistent asthma who have IgE-mediated disease not controlled by inhaled corticosteroids; it is also approved for use in chronic spontaneous urticaria, also called chronic idiopathic urticaria (3). Omalizumab has been approved for use by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In addition to reducing free IgE, other mechanisms of action, including changes in eosinophil and T-cell function as well as reduction of FcεRI expression on dendritic cells, mast cells, and basophils, have been described. There is a newer high-affinity anti-IgE, ligelizumab that has been reported to inhibit allergen-induced early asthmatic response (4). Quilizumab targets the M_1-prime segment of membrane-expressed IgE; there is a report of efficacy and safety in adults with inadequately controlled allergic asthma (5).

TABLE 38.1 NOVEL IMMUNOLOGIC THERAPIES

TARGET MOLECULE	DRUG	MECHANISM	DISEASE	DEVELOPMENT STAGE
IgE	Omalizumab	Anti-IgE	Allergic asthma Urticaria	FDA and EMA approved

	Ligelizumab	Anti-IgE	Allergic asthma	Phase II
	Quilizumab	Anti-M$_1$ prime segment of membrane-expressed IgE	Allergic asthma	Phase II
IL-4, IL-13	Pascolizumab	Anti-IL-4	Not effective in asthma	
	Pitrakinra		Not effective in asthma	
	Dupilumab	Anti-IL-4Rα	Eosinophilic asthma Atopic dermatitis	Phase III
	Anrukinzumab	Anti-IL-13	Asthma Ulcerative colitis	Phase II
	Lebrikizumab	Anti-IL-13	Asthma with high periostin	Phase III
	Tralokinumab	Anti-IL-13	Asthma with high periostin and DPP-4	
IL-5	Mepolizumab	Anti-IL-5	Eosinophilic asthma	FDA and EMA approved
	Reslizumab	Anti-IL-5	Eosinophilic asthma	FDA and EMA approved
	Benralizumab	Anti-IL-5Rα	Eosinophilic asthma	Phase III
IL-9	MEDI-528	Anti-IL-9	Not effective in	

			asthma	
	Enokizumab	Anti-IL-9	Not effective in asthma	
IL-12, IL-23	Ustekinumab	Anti-p40	Atopic dermatitis	Approved for psoriasis by FDA and EMA
IL-17	Secukinumab	Anti-IL-17A	Not yet studied in neutrophilic asthma	Approved for psoriasis by FDA and EMA
TSLP	AMG-157	Anti-TSLP	Asthma	Phase III
TNF	Infliximab	Anti-TNP	Not effective in asthma	
Interferon	Interferon γ1b	Increase T_H1	CGD	FDA approved for CGD
Chemokines	BMS-639623	Anti-CCR3	Not effective in asthma	
	GSK2239633	Anit-CCR4	Not effective in asthma	
Kinase transcription factors	R343	Anti-Syk	Not effective in asthma	
	AUT-01	Anti-STAT1	Not effective in asthma	
CRT_H2, PGD_2	QAW039 (fevipiprant)	CRT_H2 antagonist	Asthma	Phase II
	AZD1981	CRT_H2	Asthma	Phase II

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		antagonist		
Muscarinic receptors	Glycopyrrolate	Ultra long-acting muscarinic antagonist	COPD	Phase II
	Darotropium bromide	Ultra long-acting muscarinic antagonist	COPD	Phase II
Selectins	Bimosiamose	Pan-selectin antagonist	COPD	Phase II
Glucocorticoid receptors	AL-438 is an example of a SEGRAM	More transrepression with less transactivation	Not effective in asthma	

CCR3, CC chemokine receptor-3; COPD, chronic obstructive pulmonary disease; CRT$_H$2, chemokine receptor T helper type 2 cells; EMA, European Medicines Agency; FDA, Food and Drug Administration; IgE, immunoglobulin E; IL-4, interleukin 4; PGD$_2$, prostaglandin D$_2$; SEGRAM, selective glucocorticoid receptor agonists and modulator; Syk, spleen tyrosine kinase; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoeitin.

In a ragweed rhinitis trial using omalizumab, some symptomatic improvement was described in patients who had markedly reduced free IgE levels and markedly increased bound IgE levels (6). Trials of omalizumab for atopic dermatitis have reported both positive and negative results (7,8). To date, there have been no reports of omalizumab inducing an antibody response in humans. Although the most common side effect has been the development of urticarial eruptions, patients have developed other adverse effects, including the rare possibility of anaphylaxis (9).

Anti-interleukin-4 and Anti-interleukin-13

The receptor for IL-4 and IL-13 shares the same IL-4Rα chain. The common γ chain is the other half of the IL-4 receptor, whereas the IL-13Rα1 chain is the

other half of the IL-13 receptor. Both cytokines share signaling pathways and are involved in eosinophil activation and IgE synthesis (10). The anti-IL-4 monoclonal antibody, pascolizumab, was well tolerated but not efficacious (11). Pitrakinra, an anti-IL-4Rα/IL-13Rα, failed to demonstrate significant efficacy in asthma (12). There have been reports of safety and efficacy of dupilumab, an anti-IL-4Rα monoclonal antibody, in both persistent eosinophilic asthma and moderate-to-severe atopic dermatitis (13,14).

Anrukinzumab is an anti-IL-13 being tested in asthma and ulcerative colitis (15). Another anti-IL-13, lebrikizumab, has been reported to be efficacious in asthma, particularly in those subjects with high levels of periostin (16). Tralokinumab also binds soluble IL-13 and has been reported to be efficacious in severe, uncontrolled asthma, only in those subjects with high levels of periostin and dipeptidyl peptidase-4 (17).

Anti-interleukin-5

IL-5 is a helper T-cell type 2 (T_H2) cytokine that is reported to be essential for the recruitment and proliferation of eosinophils in the allergic inflammatory response. In animal models, anti-IL-5 blocking antibody has been reported to inhibit eosinophil recruitment and ablate the late-phase response (18). Two humanized anti-IL-5 blocking antibodies, mepolizumab and reslizumab, have been approved as add-on therapy for treatment of severe eosinophilic asthma by the FDA (19). An anti-IL-5Rα monoclonal antibody, benralizumab, has been reported to be safe and effective in severe eosinophilic asthma in phase III trials (20). Anti-IL-5 agents have been used off label for treatment of hypereosinophilic syndrome (HES). It should be noted that there are subgroups of HES, individuals with FIP1L1-PDGFRA fusion gene (F/P+ variant) or increased IL-5 production by a clonally expanded T-cell population (lymphocytic variant), most frequently characterized by a $CD3^-CD4^+$ phenotype. For F/P+ patients, imatinib, an LMW tyrosine kinase inhibitor, has become first-line therapy.

Anti-interleukin-9

Both activation of T_H2 cells and differentiation of mast cells are roles played by IL-9. An anti-IL-9 monoclonal antibody, enokizumab (MEDI-528), was initially reported to have possible clinical efficacy. However, further trials failed to reach efficacy endpoints (21). There are no current trials of anti-IL-9 agents for asthma or related diseases.

Anti-interleukin-12 and Anti-interleukin-23

IL-12 and IL-23 which are involved in T-cell effector function have a common subunit, p40. The receptors for IL-12 and IL-23 are found on dendritic cells and activated T cells that are thought to be important in mediating asthma, atopic dermatitis, and related diseases. Ustekinumab is a monoclonal antibody against p40 and has been approved by both EMA and FDA to treat psoriasis. There are reports of efficacy in atopic dermatitis but no randomized trials (22).

Anti-interleukin-17

IL-17 may play a role in neutrophilic, steroid-resistant asthma (23). Secukinumab, a monoclonal antibody against IL-17A, has been approved for psoriasis and ankylosing spondylitis. Although there was no efficacy in an asthma trial of brodalumab, a human anti-IL-17 receptor monoclonal antibody, there may be a subgroup of asthma patients with high levels of IL-17 in whom anti-IL-17 therapy would be efficacious (24).

Thymic Stromal Lymphopoeitin

Thymic stromal lymphopoeitin (TSLP) is a cytokine produced by epithelial cells; it initiates and promotes T_H2 responses. The receptor for TSLP is known to be present on eosinophils, basophils, mast cells, and type 2 innate lymphoid cells (25). AMG-157 is a monoclonal antibody directed against TSLP and has demonstrated efficacy in reducing allergen-induced early- and late-phase bronchoconstriction (26). There are ongoing trials using AMG-157 as an adjunct to cat immunotherapy.

Anti–Tumor Necrosis Factor α

It is well recognized that tumor necrosis factor α (TNF-α) is involved in the inflammation of certain T_H1-associated diseases like psoriasis and rheumatoid arthritis. In those diseases, anti-TNF-α therapies have produced significant clinical improvement. In patients with severe, steroid-dependent asthma, TNF-α may be upregulated as well, resulting in the recruitment of neutrophils and eosinophils into the airways (27). While there was initial enthusiasm for anti-TNF-α therapy, this has been dampened by concerns over safety. Moreover, the efficacy of anti-TNF-α therapy is likely to be confined to a small subgroup of patients with severe asthma that have high levels of TNF-α in sputum (28).

Interferons

Recombinant interferon-γ (IFN-γ) is available as a therapy approved by the FDA for chronic granulomatous disease (29). IFN-γ is known to suppress IgE production and to downregulate the function and proliferation of $CD4^+$ T_H2 cells (24). The role of interferons in IgE-mediated diseases is essentially nonexistent because the risk for side effects, including fever, chills, headache, rash, depression, and even suicide, generally outweigh any possible benefit (30). Clinical improvement has been reported in patients with severe atopic dermatitis (31). As described earlier, there are safer novel agents to treat IgE-mediated disease, like allergic asthma.

Inhibitors of Chemokines

Chemokines play important roles in migration of a variety of cells, including mast cells, basophils, eosinophils, and T_H2 cells. CC chemokine receptor-3 (CCR3) is particularly important in eosinophil migration. The LMW anti-CCR3 agent, BMS-639623, and the CCR4 antagonist, GSK2239633, have been studied in clinical trials for asthma (32–34). There are no current trials of antichemokine biologics or LMW agents for asthma, atopic dermatitis, or related diseases.

LOW MOLECULAR WEIGHT PHARMACOLOGIC AGENTS

Inhibitors of Kinases and Transcription Factors

A variety of kinase pathways can activate downstream transcription factors in the airway, resulting in activation of many cell types and production of a number of inflammatory mediators (35). Spleen tyrosine kinase (Syk) controls an important pathway in airway mast cell activation and degranulation (36). LMW Syk inhibitors R112 and R343 have been reported to reduce symptoms in allergic rhinitis and asthma (37). Signal transduction activator of transcriptions (STAT) proteins are responsible for transmitting intracellular signals initiated by cytokines. T_H2 cytokines IL-4 and IL-13 result in STAT6 activation (38); T_H1 cytokines result in STAT1 activation. A STAT1 oligonucleotide AVT-01 has been reported to be in a phase II clinical trial for asthma (39). However, there are no ongoing trials of Syk inhibitors or STAT antagonists.

Prostaglandin D$_2$ Receptor 2

A major receptor for prostaglandin D_2 (PGD_2) is the DP_2 receptor, also known as the chemoattractant receptor-homologous molecule expressed on T helper

type 2 cells (CRT_H2). Through that receptor, PGD_2 is able to induce T_H2 recruitment and activation. It is thought that PGD_2 is an important mediator of the inflammation that characterizes such diseases as allergic rhinitis and aspirin-exacerbated respiratory disease. Two LMW CRT_H2 antagonists, QAW039 (fevipiprant) and AZD1981, are being evaluated in allergic asthma (40,41).

Muscarinic Receptors

There is increased parasympathetic activity in the setting of asthmatic inflammation; hence, antimuscarinic agents such as tiotropium, umeclidinium, and aclidinium are already approved for use in in chronic obstructive pulmonary disease (COPD). Airway smooth muscle cells express both M_2 and M_3 receptors; mucous production is caused primarily by M_3 receptors (42). Newer antimuscarinic agents being studied for asthma and COPD are more M_3 selective and very long lasting (43). They include glycopyrrolate and darotropium bromide (44,45).

Selectins

There are three selectins which are cell-adhesion glycoproteins; E-selectin, L-selectin, and P-selectin are present on endothelium, leukocytes, and platelets, respectively (46). Selectins are capable of inducing cell activation and, therefore, are a target for suppressing allergic inflammation. A pan-selectin antagonist, bimosiamose, has been reported to reduce sputum eosinophils and late-phase reactions. Although there are no ongoing trials in asthma, bimosiamose has been reported to be a promising LMW therapeutic agent in the treatment of COPD (47).

Other Molecular Targets in Allergic Disease

There is interest in the development of novel glucocorticoid compounds that would retain the transrepressing actions of the glucocorticoid receptor which are thought to be important for anti-inflammatory actions. These new glucocorticoids would have relatively little transactivating activity, assumed to be responsible for the undesirable side effects. These compounds are classified as selective glucocorticoid receptor agonists (SEGRAs) or selective glucocorticoid receptor modulators (SEGRMs). SEGRAs and SEGRMs are collectively called selective glucocorticoid receptor agonists and modulators (SEGRAMs) (48). One such compound is AL-438 which caused less hyperglycemia and less inhibition of bone formation than prednisone in a rat

model (49). No successful human SEGRAMs have yet been reported.

Bitter taste receptors (TAS2Rs) have recently been found to be expressed on human airway smooth muscle. The activation of TAS2Rs results in marked smooth muscle relaxation (50). It has been suggested that compounds which would activate TAS2Rs could be a new class of bronchodilators in the treatment of obstructive lung diseases because they act differently than β-agonists or antimuscarinics. No such agents have yet been reported.

PROBIOTICS

According to the World Health Organization Expert Consultation Report of 2001, probiotics are "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (51). Although there is a reasonable rationale for anticipating benefits from probiotics, there are currently no positive recommendations from any international medical society to use probiotics or prebiotics-nutrients that probiotics need for the treatment or prevention of food allergy (52). There are also no recommendations relative to preventing allergic rhinitis or asthma. There are conflicting recommendations for prevention of eczema in high-risk infants (52). Although there have been several studies reporting a benefit with probiotics in prevention of atopic disease such as eczema, other studies have failed to support this (53). None of the studies has shown any clear preventive effect on sensitization, nor any benefit in any allergic disease other than atopic dermatitis.

The term *probiotic* is often used loosely to include bacterial strains with little documented immunomodulatory capacity or controlled studies to support the claims. It is not known whether effects in experimental systems have any clinical relevance. Finally, little is known about the large, complex gut ecosystem. Explanations for the varied results among studies include host factors such as genetic differences in microbial responses and allergic predisposition. The variable reported results may also be caused by environmental factors, including the preexisting microbial gut flora, individual organisms chosen to include in the probiotic, diet, and treatment of the host with antibiotics (54).

Clinical studies continue to be performed and reported. Hopefully there will be a better understanding of which individuals will likely benefit from which probiotics, as studies, including careful characterization of subjects and probiotic composition, are conducted.

CONCLUSION

Novel immunologic therapies offer the hope of true revolutions in treatment of asthma and allergic-immunologic disorders. Knowledge gained from basic research has led to potential therapies, but the clinical effectiveness remains to be established. When an antagonist or a biologic modifier becomes available, its administration helps to reinforce or minimize the contribution of the agonist or biologic reactant to disease processes. For example, platelet-activating factor (PAF) is known to be a bronchoconstrictor agent and is a potent chemotactic factor for eosinophils. To date, PAF antagonists have had modest effects on inhibiting allergen-induced as opposed to PAF-induced bronchial responses. Thus, the contribution of PAF to allergen-induced bronchial responses seems less than initially anticipated based on the potency of PAF as a bronchoconstrictor agonist.

Novel therapies need to be safe if widespread use is planned. Physicians will need to be aware of possible unexpected positive or negative effects when new therapies are used. For example, administration of novel immunologic therapy for patients with asthma and allergic rhinitis might concurrently exacerbate the patient's rheumatoid arthritis or vice versa. There will be opportunities to revolutionize therapy, and learning how best to use the novel agents will involve pharmacologic studies, clinical trials, effectiveness studies, and post licensing surveillance.

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SECTION X

Special Situations

CHAPTER 39

Allergic Disorders in Pregnancy
PAUL A. GREENBERGER

INTRODUCTION

The major conditions that the allergist-immunologist diagnoses and treats can occur in the context of gestation or in anticipation of pregnancy. Examples include asthma, allergic and nonallergic rhinitis, acute or chronic rhinosinusitis, nasal polyposis, urticaria, angioedema, anaphylaxis, and immunodeficiency. Goals of managing gravidas should include effective control of the underlying allergic-immunologic conditions; avoidance measures; guidance on medications, diets, and supplements; action plans or preparedness for emergencies such as acute severe asthma or anaphylaxis; and communication between the physician managing the allergic-immunologic conditions and the physician managing the pregnancy.

ASTHMA

Asthma occurs in 3.7% to 8.4% of pregnancies in the United States (1–3) and in up to 12.4% of pregnancies in Australia (4) and 12.3% in Canada (5). Asthma may have its onset during gestation and present as acute severe asthma, requiring hospitalization. Wheezing dyspnea may result in interrupted sleep, persistent coughing, hypoxemia, and even rib fractures during gestation. The sequelae of

ineffectively controlled asthma on the gravida can be devastating in that maternal deaths may occur in the most extreme cases (6,7). Other untoward outcomes of asthma during gestation include fetal loss (abortions or stillbirths), increased rate of preterm deliveries (<37 weeks' gestation), intrauterine growth retardation (<2,400 g), antepartum and postpartum hemorrhage, gestational hypertension, preeclampsia, oligohydramnios, and hyperemesis gravidarum (1,2,8–17). Not all studies report all the listed complications. There is a troubling report of acute exacerbations of asthma during the first trimester being associated with an increased risk of congenital malformations (18). Repeated episodes of acute severe asthma during gestation have resulted in hypoxemic effects on the fetus. There is a report of pregnancy termination because of life-threatening acute severe asthma (19). Conversely, with cooperation between the gravida and physician managing the asthma and effective asthma control, there can be successful outcomes for most women (1,2,8–18,20–22). Prevention of acute severe asthma has been associated with pregnancy outcomes approaching that of the general population (9). Use of inhaled corticosteroids (1,2,9–18,20) has been effective as has prednisone in managing even the most severe cases of asthma during gestation. Some studies have reported small (100 to 200 g) reductions in birth weight in gravidas who had used prednisone. Other studies have found essentially normal outcomes despite administration of prednisone as long as there was avoidance of hospitalizations and emergency care (9,22–24).

Exacerbations of asthma during gestation may result in more hospitalizations than in nonpregnant patients with asthma. One mechanistic explanation is that there is reduced respiratory reserve in gravidas with asthma. It is also possible that they may receive less than recommended treatment because they are pregnant. The 2008 American College of Obstetrics-Gynecology Practice Bulletin (2) and the National Asthma Education and Prevention Program Expert Panel Report (1,25) advise oral corticosteroids for treatment of acute episodes of asthma as part of a stepwise approach.

PHYSIOLOGIC CHANGES DURING GESTATION

Although the frequency of respiration is not changed, tidal volume increases in pregnancy (26,27). The minute ventilation rises 19% to 50% by late pregnancy (28–30). Vital capacity is unchanged, unless there is an exacerbation of asthma. Oxygen consumption increases by 20% to 32%. Large increases in progesterone and estrogen produce a respiratory alkalosis from greater minute ventilation attributable to increased carotid body sensitivity to hypoxia (31). These changes occur before there is significant enlargement of the uterus. Arterial blood gas

concentrations reflect a compensated respiratory alkalosis with pH ranging from 7.40 to 7.47 and partial pressure of carbon dioxide (PCO_2) from 25 to 32 mm Hg (30,32). The maternal partial pressure of oxygen (PO_2) ranges from 91 to as high as 106 mm Hg (30,32). The near-term alveolar–arterial oxygen gradient is 14 mm Hg in the sitting position compared with 20 mm Hg in the supine position. An explanation for the larger alveolar–arterial oxygen gradient when supine is decreased cardiac output because the enlarging uterus compresses the inferior vena cava which reduces venous return. Especially in the third trimester, gravidas should try to avoid sleeping supine and practicing yoga positions where there is reduced venous return or outright hypotension (33).

Total lung capacity is unchanged or reduced by 4% to 6%. The gravida breathes at reduced lung volumes because residual volume and functional residual capacity (FRC) are decreased. The diaphragm moves cephalad (28). As with the development of maternal hyperventilation, the residual volume and FRC decline before significant uterine enlargement occurs. The diaphragm flattens during gestation, and there is less negative intrathoracic pressure reported in some studies. One could speculate that early airway closure would occur if there were less negative intrathoracic pressure. Because during episodes of acute asthma, the gravida with asthma generates large negative intrathoracic pressures to apply radial bronchodilating traction, any decline in ability to develop more negative inspiratory pressures would predispose gravidas with asthma to more sudden deterioration because of airway closure.

Bronchial responsiveness to methacholine does not change in a clinically important way; however, a statistically significant change has been reported with PC_{20} increasing from 0.35 to 0.72 mg/mL from preconception to postpartum (34). In this study of gravidas with mild asthma, the forced expiratory volume in 1 second (FEV_1) improved by 150 mL, and the FEV_1 increased from 82% to 87% (34). The increase in serum progesterone concentration during gestation did not correlate with improvement in bronchial responsiveness (35). Although progesterone relaxes smooth muscles of the uterus and gastrointestinal tract, these findings suggest that factors other than progesterone contribute to changes in bronchial responsiveness.

Other Physiologic Changes

Cardiac output increases by 25% at 6 weeks and in later pregnancy can rise 30% to 60% because of the increase in heart rate and reduced vascular resistance (36,37). The latter results from estrogen supported generation of nitric oxide

(38). The decrease in systemic vascular resistance is accompanied by an increase in the heart rate from 10 to 20 beats/minute. Stroke volume increases little; the uterine blood flow rises as much as 10-fold, from 50 to 500 mL/minute at term (32). The blood volume increases an average of 1,600 mL, and gravidas appear vasodilated as total body water expands by 1 to 5 L (36,37,39). Because of avid retention of sodium, gravidas are sensitive to overzealous fluid administration. Although correcting any dehydration is indicated, injudicious fluid replacement has resulted in acute pulmonary edema with normal cardiac function. During the latter half of gestation, these changes become manifest because the gravida has increased preload (mild volume overload with activation of the renin–angiotensin–aldosterone system), increased chronotropy, and reduced afterload (32,36,37,39).

Even though during gestation there is a 20% to 40% increase in erythrocyte mass, the maternal hemoglobin concentration decreases (31,32). The increase in erythrocyte mass is offset by the even larger increase of plasma volume, resulting in relative anemia.

FETAL OXYGENATION

The vascular resistance of uterine vessels (progesterone, nitric oxide, and prostaglandin effects) declines so that there can be the large increase in uterine blood flow (40). The fetus survives in a low-oxygen environment with little reserve oxygen store, should the supply of oxygen-rich uterine blood be compromised. Animal and human studies demonstrate reduced fetal oxygenation if there is reduced uterine blood flow that may occur with severe maternal hypotension, hypocarbia, or shock (32). Maternal hyperventilation can reduce venous return and shift the maternal oxyhemoglobin dissociation curve to the left. Modest declines in maternal oxygenation seem to be tolerated satisfactorily by the fetus, but substantial degrees of maternal hypoxemia may threaten survival of the fetus. Uterine vessels during gestation are dilated maximally based on experimental data, primarily from pregnant sheep and from some human studies. Uterine vessels do not vasodilate after β-adrenergic agonist stimulation, but do vasoconstrict from α-adrenergic agonists. Some obstetric anesthesiologists administer ephedrine 25 to 50 mg intravenously if hypotension occurs during epidural anesthesia. The β-adrenergic effects of ephedrine result in increased cardiac output, which increases systolic blood pressure and maintains uterine perfusion. Intramuscular epinephrine provides primarily β-adrenergic stimulation, whereas intravenous epinephrine results in mostly β and some α effects.

The fetal hemoglobin is 16.5 g/L, and the oxygen pressure at which hemoglobin is 50% saturated is 22 mm Hg in the fetus, in contrast to 26 to 28 mm Hg in the gravida (32). Fetal umbilical venous PO_2 measurements at term average about 32 mm Hg, with PCO_2 49 mm Hg. There is a very large shunt effect of the uteroplacental circulation; this is demonstrated when the gravida inspires 100% oxygen in the absence of acute asthma, fetal umbilical venous PO_2 increases to 40 mm Hg and PCO_2 is 48 mm Hg (41). Such changes in PO_2 can be quite important for the fetus in distress, although the uteroplacental shunt is large. For the same incremental increases in arterial PO_2, the leftward shift of the fetal hemoglobin oxygen dissociation curve results in larger increases in fetal oxygen saturation than in maternal blood.

In summary, fetal oxygen delivery depends on many factors, but most critical are blood flow (maternal cardiac output) to the uterus, integrity of the placenta, and maternal arterial oxygen content.

EFFECTS OF PREGNANCY ON ASTHMA

For the individual gravida, it is not always possible to predict the effects of pregnancy on asthma. Studies in the literature report varying degrees of improvement, deterioration, or no change in the clinical course (2,42). Over the past five decades, the published reports appear to be rather consistent, with approximately equal proportions of patients being unchanged, improving, or deteriorating. In a review from 1980 of nine studies involving 1,059 pregnancies, 49% of gravidas were unchanged in terms of severity of asthma, 29% improved, and 22% worsened (42). A prospective study of 198 pregnancies in 1988 recorded somewhat similar results in that 40% of gravidas had no change in medications, 18% of gravidas required fewer medications, but 42% required more medications (43). Similarly, using medication and symptom diary cards, during 366 gestations in 330 gravidas with mild or moderate asthma, asthma was unchanged in 33%, improved in 28%, and worsened in 35% (44). In a prospective study of 873 gravidas with asthma from 2003, 44% had no symptoms or treatment during the pregnancy, 32% had intermittent asthma, and 23% were considered to have persistent asthma (mild 13%, moderated 7%, and severe 4%) (11). How effective is the asthma control? In a series of 2,123 gravidas with asthma, about 33% had acute "unscheduled" care ranging from office visits to hospitalizations (45). It is not known whether ineffectively controlled asthma contributed, but there is a report of an association between maternal asthma and intellectual disability in children (46,47). The association

was also increased in the presence of maternal diabetes, renal or urinary tract conditions, and epilepsy (46,47).

Pregnancy in adolescents with asthma has been associated with many emergency department visits and hospitalizations for asthma (48). Some adolescents with severe asthma may not benefit from the prescription of anti-inflammatory medications because of poor adherence (48). The combination of poverty, inadequate or no prenatal care, limited education, and not being able to make control of asthma a priority can complicate pregnancies at any age of the gravida but especially during adolescent pregnancies.

Cigarette smoking during gestation can have long-term effects. Maternal smoking of 20 or more cigarettes/day in utero was associated with current asthma in 14-year-old girls but not in 14-year-old boys (49). These findings support the persistence of harmful effects of smoking in utero even if the gravida then quits after she delivers. Adverse effects on the child's lung function, FEV_1 and FEF_{25-75} and FEV_1/forced vital capacity, have been demonstrated in 7- to 18-year-olds whose mothers smoked during pregnancy or where another member (but not the gravida) smoked during the pregnancy (50). Clearly, gravidas must not smoke during gestation for their own well-being and that of their children, who could have loss of lung function (51).

CHOICE OF THERAPY

The approach to therapy includes making an assessment of the level of control, severity, and risks (1,2,9,23,52,53) (Table 39.1). Specifically, it should be determined (a) whether the gravida has near fatal (potentially fatal) asthma (54), (b) whether allergens in the home or workplace are contributing, and (c) whether the gravida is likely to be adherent to the recommendations provided.

Avoidance Measures

General avoidance measures include cessation of smoking and preferably recommending that there be no secondhand smoking in the home environment. There should be no or very minimal consumption of alcoholic beverages, cessation of illicit drug use, and avoidance of drugs with teratogenic or harmful potential. Examples of these include tetracyclines (discoloration of infant's teeth from insufficient production of enamel), sulfonamides in the last trimester (glucose-6 phosphate dehydrogenase [G6PD] deficiency could cause hemolytic anemia), troleandomycin, clarithromycin, methotrexate, mycophenolate mofetil, and antibiotics such as quinolones.

TABLE 39.1 GOALS OF THERAPY FOR MANAGEMENT OF THE GRAVIDA WITH ASTHMA

- Prevent maternal fatalities and fetal demise
- Maximize asthma control
- Prevent hospitalizations, emergency department visits, and unscheduled care visits
- Prevent/reduce nocturnal asthma
- Prevent/reduce limitations of activities, school or work absenteeism/presenteeism
- Maximize respiratory status and pulmonary function
- Use appropriate medications
- Prepare an action plan for exacerbations

When there is allergic asthma, individual avoidance measures should be implemented for animals, dust mites, cockroaches, and fungi. Aspirin and nonsteroidal anti-inflammatory drugs should be withheld in the gravidas with aspirin-exacerbated respiratory disease. However, nonselective anti-inflammatory drugs, such as ibuprofen, naproxen, or diclofenac (55,56), are considered appropriate for the first 30 weeks of gestation, if indicated for aspirin-tolerant gravidas. They should be avoided after that time because of the risk of closure of the fetal ductus arteriosus causing pulmonary hypertension. Acetaminophen is acceptable.

Medications

In 2015, the US Food and Drug Administration (FDA) replaced the pregnancy risk letter categories on prescription and biologic drug labeling with new information in an attempt to make them more meaningful to both patients and health care providers; until that is integrated into the medical system, letter grades will continue. In human gestation, organogenesis is proportionately relatively short (days 12 to 56) compared with animals. Drugs are infrequent causes of major congenital malformations, which have an overall rate of 3% to 7% (57), depending on the studies and degree of ascertainment 10.1% (5). About two-thirds of malformations are from unknown factors, and an additional 25% are genetically determined. About 5% of malformations have been associated with environmental factors, including medications, maternal infections, and radiation.

There are increasing data to justify the appropriate use of many medications

for treatment of asthma and its comorbidities during gestation (Table 39.2) (1,2,9,11,12,20,21,23–25,32,52,53,58–60). Where feasible, it is preferable to use inhaled as opposed to oral medications; to some extent, this point has become moot in that there are data to justify appropriate use of oral medications.

Examples of teratogenic agents include ethanol, isotretinoin, phenytoin, carbamazepine, valproic acid, angiotensin-converting enzyme inhibitors, diethylstilbestrol (vaginal carcinoma), thalidomide, inorganic iodides, lithium carbonate, tetracycline, doxycycline, streptomycin, mycophenolate mofetil, and some antineoplastic drugs that have not caused fetal loss earlier. Erythromycin has been associated with an increase in cardiac malformations, and clarithromycin has an FDA pregnancy category C rating.

Most to almost all medications for use for asthma are considered appropriate for treatment in pregnancy from the benefit to risk perspective (1,2,9,11,12,20,21,23–25,32,52,53,58–60).

Human data on the use of oral corticosteroids have not identified teratogenic effects for prednisone, methylprednisolone, or hydrocortisone, and they are recommended when indicated (1,2,9,20,23–25,52,53). The inhaled corticosteroids for which there are the most published data are beclomethasone dipropionate, budesonide, and fluticasone. Budesonide is the only inhaled corticosteroid with an FDA pregnancy category B rating. Most gravidas with mild persistent and some with moderate persistent asthma will be managed effectively with monotherapy with inhaled corticosteroids. The American College of Obstetricians and Gynecologists Practice Bulletin (2) concluded that "budesonide is the preferred inhaled cortiocosteroid for use in pregnancy." The National Asthma Education and Prevention Program (NAEPP) Working Group took a view that "inhaled corticosteroids other than budesonide may be continued in patients who were well controlled by these agents prior to pregnancy especially if it was thought that changing formulations may jeopardize control" (1).

Oral steroids should be initiated early during exacerbations, because doubling of the inhaled corticosteroid from whatever was the controlling dosage often is ineffective unless the controlling dosage was "pediatric," such as budesonide 200 to 400 μg/day. In a study of nonpregnant patients who were managed with a mean dose of beclomethasone dipropionate of 710 μg/day, the approach tried was that of doubling the inhaled corticosteroid when there were 15% or greater reductions of peak expiratory flow rates or increased symptoms (61). This approach did not prevent the need for oral corticosteroids, which were initiated

when the peak expiratory flow rate decreased by 40% (61). Therefore, the gravida should be aware that the inhaled corticosteroid, inhaled corticosteroid/albuterol, or inhaled corticosteroid/long-acting β_2-adrenergic agonist combination may be inadequate for some exacerbations of asthma. Although this statement applies to gravidas with severe persistent asthma, it also applies to gravidas with mild or moderate persistent asthma who might experience a severe worsening of asthma when there is an upper respiratory infection.

TABLE 39.2 APPROPRIATE MEDICATIONS DURING GESTATION

ANTIASTHMA MEDICATIONS

Albuterol, levalbuterol

Salmeterol in combination with an inhaled corticosteroid

Formoterol in combination with an inhaled corticosteroid

Budesonide, beclomethasone dipropionate, fluticasone[a]

Prednisone/methylprednisolone

Cromolyn

Montelukast/zafirlukast

Nedocromil[b]

Theophylline

Epinephrine (intramuscular)

Terbutaline

Ipratropium bromide, tiotropium

ALLERGEN IMMUNOTHERAPY (SUBCUTANEOUS OR SUBLINGUAL)

INACTIVATED INFLUENZA VACCINE

ANTIRHINITIS MEDICATIONS

Budesonide, beclomethasone dipropionate, fluticasone[a]

Cromolyn

Loratadine

Cetirizine

Levocetirizine

Diphenhydramine

Chlorpheniramine

Pseudoephedrine (third-trimester only, if at all)

GASTROESOPHAGEAL REFLUX DISEASE MEDICATIONS

Lansoprazole

Esomeprazole

Rabeprazole

Cimetidine

Ranitidine

Famotidine

ANTIBIOTICS

Azithromycin

Penicillin derivatives

Cephalosporins

Clindamycin

Nitrofurantoin

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[a]Mometasone and ciclesonide have favorable, very topical properties, and appear suitable for administration in pregnancy. The decision can be made on a case-by-case basis.

[b]Not available (currently).

Cromolyn (32) has a very long record of use for asthma (allergic rhinitis and allergic conjunctivitis) and can be recommended for intermittent or mild, moderate or even severe persistent asthma. It can be effective as prophylactic treatment before exercise, cold air and/or fume exposure, pet dander, and dust or mold exposures. However, it remains available for administration for asthma only by nebulization. Nedocromil (62,63) also inhibits early and late bronchial

responses to allergens as does cromolyn, and both are (were) labeled FDA pregnancy category B. Nedocromil is not available for treatment of asthma, because it has not been reformulated to be free of chlorofluorocarbons.

Leukotriene antagonists, montelukast and zafirlukast, are designated as FDA pregnancy category B and are recommended (1,2,25,52,53,58,59) for moderate and persistent asthma as alternative treatments. It is informative that in two series, investigators did not identify an increased risk of teratogenicity (58,59). There are insufficient data to support administration of zileuton, a 5-lipoxygenase inhibitor in pregnancy. Zileuton is FDA pregnancy category C, based on animal studies (62).

Albuterol is recommended as the short-acting β_2-adrenergic agonist of choice (1,2,23,25,52,53). The NAEPP Working Group advises that for acute exacerbations of asthma, "up to 3 treatments of 2–4 puffs by MDI at 20-minute intervals or single nebulizer treatment" can be started at home (25). The author would suggest that albuterol be limited to two inhalations and prednisone 40 to 60 mg initiated instead of up to 12 inhalations in the first hour if there is no physician present. If the gravida remains quite dyspneic, she should seek emergency department or perhaps office assessment and care.

Some gravidas with severe asthma during pregnancy may require low- to moderate-dose prednisone administered on an alternate-day basis to maintain effective asthma control. Experience with alternate-day prednisone, along with intermittent courses of daily prednisone (40 to 60 mg each morning for 5 to 7 days) for exacerbations, has resulted in avoidance of emergency department visits and hospitalizations and normal pregnancy outcomes, such as newborn birth weight, head circumference, and length (9,10,24).

Muscarinic antagonists, including the short-acting, ipratropium bromide for acute asthma, and the long-acting, tiotropium, for persistent, steps 4 and 5 asthma, are appropriate for administration in pregnancy (52) in that benefits/risk support their use.

Theophylline is not contraindicated for treatment of asthma during gestation, but has a narrow therapeutic index and is considered an alternative therapy (2). Its metabolism is altered by many factors, and drug interactions must be considered. The peak serum concentration should be in the range of 5 to 12 μg/mL.

Immunobiologics

In a prospective, observational study, where 188 of 191 women received at least a single dose of omalizumab, the rate of major congenital malformation was 4.4% without a specific pattern of anomaly identified (21). The rates for prematurity (14.5%), small for gestational age (10.9%) and low birth weight, full-term infants (3.2%), were comparable to other studies of asthma during pregnancy. These data support the administration of omalizumab as add-on therapy. It has an FDA pregnancy category B rating.

There aren't data or expert opinion regarding other immunobiologics, including mepolizumab and reslizumab. For women who become pregnant while receiving these therapies, they should contact https://mothertobaby.org to register.

Allergen Immunotherapy

Allergen immunotherapy can be continued or even initiated during pregnancy. The only recognized risk from allergen immunotherapy is anaphylaxis. There are no data to suggest that women are more likely to experience anaphylaxis from subcutaneous allergen immunotherapy (SCIT) when pregnancy occurs. Data from 121 pregnancies in 90 gravidas receiving SCIT showed a low incidence of anaphylaxis (64). In 2011, the Joint Task Force on Practice Parameters of the American Academy of Allergy, Asthma and Immunology (AAAAI), American College of Allergy, Asthma and Immunology (ACAAI), and Joint Council of Allergy, Asthma and Immunology (65) commented as follows:

Summary Statement 20a: Allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. C

Summary Statement 20b: If pregnancy occurs during the build-up phase and the patient is receiving a dose unlikely to be therapeutic, discontinuation of immunotherapy should be considered. D

The author believes that as long as the gravida is not having systemic reactions to SCIT, she can have the dosage increased in the normal manner. Indeed, the goal of any aeroallergen immunotherapy is to reduce the symptoms, need for medications, and improve the quality of life. Unfortunately, SCIT does not protect the fetus from subsequent development of atopic disorders (66).

One would anticipate that sublingual, aeroallergen immunotherapy (SLIT) would be safe and appropriate during pregnancy. The package inserts for grass and ragweed products in the United States note that the products should be used "only if clearly needed." Presumably, that is why the SLIT was initiated in the

first place. However, an expert report suggests to hold dosages if newly pregnant (67). The physician or health care professional can reassess the indication and whether any troublesome local or systemic reactions are occurring. If not, the SLIT can be continued during pregnancy. It should be noted that epinephrine for self or health care professional administration is considered appropriate in pregnancy (32).

ACUTE ASTHMA

As in managing the nonpregnant patient with asthma, exacerbations of asthma should be reversed as quickly and effectively as possible. Acute severe asthma (status asthmaticus) has been associated with intrauterine growth restriction (retardation), stillbirths, maternal deaths, and untoward effects on the fetus, such as cerebral palsy from inadequate oxygenation. The goal in treating the gravida with acute asthma is to minimize maternal hypoxemia, hypocarbia, or respiratory acidosis and to maintain adequate oxygenation for the fetus.

β_2-Adrenergic agonists (such as albuterol) are the drugs of choice for home or emergency department/hospital use (1,2,23,52,53). If the gravida presents in the emergency department and the initial response to albuterol is incomplete, oral or intravenous corticosteroids should be administered promptly. Continued acute severe dyspnea may necessitate continued nebulized therapy or additional albuterol by metered-dose inhaler. There must be monitoring of oxygen and overall respiratory status. Ipratropium bromide may be administered with albuterol (52). Some gravidas with very severe dyspnea will not respond to albuterol or ipratropium bromide administered by nebulizer or metered-dose inhaler; in that setting, epinephrine can be administered intramuscularly as 0.3 mL (1:1,000). The justification for epinephrine is that: (a) it is synthesized endogenously, (b) it is not teratogenic, (c) it is metabolized rapidly, (d) its onset of action is rapid, and (e) variables associated with drug delivery by inhalation do not have to be considered. The use of epinephrine for acute asthma or anaphylaxis increases cardiac output, which can maintain uterine perfusion in contrast to the fear that epinephrine will cause fetal loss by decreasing uterine blood flow. The adverse effects of acute severe asthma (or anaphylaxis) can be a serious threat to the gravida or fetus.

The NAEPP Expert Panel Report suggested that home treatment of the acute exacerbation could include inhaled β_2-adrenergic agonist (albuterol) therapy from two to four inhalations every 20 minutes in the first hour or as a single nebulizer treatment (25). With a good response defined as peak expiratory flow

>80% of the personal best, no wheezing or shortness of breath, a response to the albuterol treatment lasting for 4 hours and no apparent drop in fetal kick counts, the gravida should continue the albuterol and double the inhaled corticosteroid for the next 7 to 10 days (25). If the gravida has an incomplete response, such as having continued wheezing and shortness of breath and the peak expiratory flow rate being 50% to 80%, an oral corticosteroid was recommended. A poor response to the initial treatment was defined as peak expiratory flow <50%, marked wheezing and shortness of breath, and decreased fetal kick activity. The gravida, in that case, should begin the oral corticosteroid, repeat the albuterol, call for medical advice, and proceed to the emergency department (25).

A personalized approach uses the level of asthma severity to guide therapy. How much medication and what types have been used in the past to control the asthma? How responsive has the asthma been? Have there been previous hospitalizations, intensive care unit admissions, or intubations? The latter two events imply a diagnosis of potentially (near) fatal asthma (53,54). If there was poor adherence in the past, it can be anticipated that guideline type of control will not be achievable. Alternative treatment plans should be considered.

When the gravida presents with moderate or severe acute wheezing dyspnea, oral corticosteroids should be administered with the initial albuterol or albuterol/ipratropium treatment. For example, prednisone 40 to 60 mg is an appropriate dosage. The initial beneficial effects may occur in 2 to 6 hours or longer. If the initial treatment is not effective over the first 2 hours, it is likely that acute severe asthma (status asthmaticus) has occurred. Hospitalization or treatment in an observation unit is indicated; theophylline has not been found to be superior to albuterol and intravenous methylprednisolone therapy. In some gravidas with acute severe asthma, it may be sufficient to monitor the pulse oxygenation measurements. In other gravidas, an arterial blood gas determination will be necessary to monitor the PCO_2 and pH. Some gravidas require fetal heart monitoring during or before discharge.

Excessive fluid replacement is not indicated, but volume depletion should be corrected. The gravida can develop acute pulmonary edema (noncardiac) from excessive crystalloid administration because she is volume expanded during gestation. The resultant acute dyspnea may be attributed to acute severe asthma when it is from fluid overload and noncardiac pulmonary edema.

When the gravida, who has experienced an exacerbation of asthma, is discharged from the emergency department, observation unit, or hospital, a short course of oral corticosteroid should be administered to prevent continued

symptoms and signs of asthma (1,2,9,20,23–25,32,52,53). In the rare setting of acute respiratory failure during acute severe asthma, an emergency cesarean delivery may be necessary (68).

■ PERSISTENT ASTHMA

Some types of persistent asthma during gestation are listed in Table 39.3. Should gravidas require daily medication, an allergy-immunology consultation is indicated to identify and address immunoglobulin E-mediated triggers of asthma, to determine whether allergic bronchopulmonary aspergillosis (ABPA) is present, and to provide expertise in the diagnosis and treatment of nasal polyps, cough, rhinitis, or rhinosinusitis. Avoidance measures are indicated to reduce bronchial hyper-responsiveness and the need for antiasthma medications.

TABLE 39.3 CLASSIFICATION OF ASTHMA DURING PREGNANCY

- Intermittent
- Persistent (allergic or nonallergic)
  - Mild
  - Moderate
  - Severe
- Potentially (near) fatal asthma
- Asthma with allergic bronchopulmonary aspergillosis
- Aspirin-exacerbated respiratory disease (aspirin intolerant asthma)
- Adolescent asthma

The goals of management include maintaining a functional respiratory status, as well as minimizing wheezing dyspnea, nocturnal asthma, exercise intolerance, emergency department visits, acute severe asthma, and maternal fatalities or loss of the fetus (Table 39.1).

Dyspnea can be sensed during gestation in the absence of asthma during the first two trimesters (69). A respiratory rate of more than 18 breaths/minute has been considered a warning sign for pulmonary pathology complicating "dyspnea during pregnancy" (69). It may be helpful to utilize the pregnancy asthma control test (range 5 to 25 with ≥20 consistent with control of asthma) which is modified to focus on dyspnea (70). Alternative acute onset comorbidities include late pregnancy, peripartum, or postpartum cardiomyopathy/congestive heart failure (71).

Many gravidas can be managed effectively with inhaled budesonide, beclomethasone dipropionate or fluticasone, and inhaled albuterol for symptomatic relief. For gravidas who have intermittent asthma or mild persistent asthma, inhaled budesonide, beclomethasone dipropionate, fluticasone, leukotriene-receptor antagonists, or, possibly, theophylline are appropriate during gestation. A short-acting bronchodilator, such as albuterol or levalbuterol, would be recommended if needed. If these drugs are ineffective because of worsening asthma, such as from an upper respiratory infection, a short course of prednisone such as 40 mg daily for 5 to 7 days may be administered. Antibiotics can be prescribed for secondary bacterial infections after viral upper respiratory infections, acute bronchitis, or exacerbations of chronic or subacute rhinosinusitis. Azithromycin, ampicillin, amoxicillin, amoxicillin-clavulanate, or cephalosporins are appropriate antibiotics (Table 39.2).

For severe persistent asthma, higher dosages inhaled corticosteroids can be used as can fluticasone/salmeterol or budesonide/formoterol (52). Higher doses of inhaled corticosteroids may produce systemic side effects. Proper inhalation technique is necessary and should be assessed periodically. Should asthma be managed ineffectively with avoidance measures and the inhaled corticosteroid/long-acting β_2-adrenergic agonist combination, then cromolyn by nebulization, leukotriene-receptor antagonists, tiotropium, or theophylline can be considered (1,2,52,53). If already being administered when the pregnancy occurs, immunobiologics such as omalizumab, mepolizumab, or reslizumab should be continued on an individualized basis.

If the gravida has significant wheezing on examination, nocturnal asthma, or major changes in spirometry or peak expiratory flow rates, a short course of prednisone may be indicated to relieve symptoms and improve respiratory status. If the gravida has improved after 1 week of prednisone, either the prednisone can be discontinued or it can be converted to alternate-day administration and tapered. The most effective antiasthma medications for chronic administration during gestation in the usual order of efficacy are prednisone, inhaled corticosteroids, and, then based on patient characteristics, inhaled β_2-adrenergic agonists (albuterol and levalbuterol), leukotriene-receptor antagonists, tiotropium, cromolyn, and theophylline. Theophylline has a low therapeutic index and, for the most part, is not considered anti-inflammatory. In some gravidas with severe persistent asthma, bronchiectasis from ABPA, or inhaled corticosteroid phobia, theophylline can be used. It is not teratogenic in humans. Comorbidities such as allergic rhinitis, rhinosinusitis, and gastroesophageal

reflux disease should be addressed (Table 39.2).

Essentially all patients can be managed successfully during gestation. Some patients with potentially (near) fatal asthma are unmanageable because of noncompliance with physician advice, medications, or in keeping ambulatory clinical appointments. Such gravidas are considered to have malignant potentially fatal asthma. Long-acting methylprednisolone (80 to 120 mg intramuscularly) is of value to prevent repeated episodes of status asthmaticus or respiratory failure. This approach should be instituted to try to prevent fetal loss or maternal death in the nearly impossible-to-manage gravida. Adequate documentation in the medical record is needed. Psychologic, psychiatric, and social work evaluations may be obtained. Gravidas with malignant potentially fatal asthma, however, may refuse evaluation or necessary therapy. The serum glucose should be determined regularly because of hyperglycemia produced by long-acting methylprednisolone. Other antiasthma medications should be minimized to simplify the medication regimen.

LABOR AND DELIVERY

When asthma is controlled effectively, the gravida can participate in prepared childbirth methods without limitation. Minute ventilation increases to as great as 20 L/minute during labor and delivery (41). Should cesarean delivery be necessary, complications from anesthesia should not create difficulty if asthma is well controlled. When the gravida has used inhaled corticosteroids or oral corticosteroids during gestation, predelivery corticosteroid coverage should include 100 mg hydrocortisone intravenously every 8 hours until postpartum, and other medications can be used. Parenteral corticosteroids suppress any asthma that might complicate anesthesia required for cesarean delivery. The prior use of recommended dosages of inhaled corticosteroids or alternate-day prednisone should not suppress the surge of adrenal corticosteroids associated with labor or during anesthesia.

When the gravida who requires regular moderate- to high-dose inhaled corticosteroids or daily or alternate-day prednisone plans to have a cesarean delivery, preoperative prednisone should be administered for 3 days before anesthesia. The gravida should be examined ideally 1 to 2 weeks before delivery to confirm stable respiratory status and satisfactory pulmonary function. In gravidas with persistent mild asthma, preanesthetic therapy can consist of 5 days of inhaled corticosteroid.

When the gravida presents in labor in respiratory distress, emergency

measures such as inhaled albuterol and oral or intravenous corticosteroids should be administered promptly. Adequate oxygenation and fetal monitoring are essential.

RHINITIS DURING PREGNANCY

Intranasal obstruction and nasal secretions can be very troublesome during gestation and interfere with sleep. It has been reported that 18% to 61% of gravidas experience symptoms of rhinitis during some time during gestation (72). Nasal congestion during gestation may be influenced by (a) increased blood volume, (b) progesterone's effects causing smooth muscle relaxation of nasal vessels, (c) estrogen's effects causing mucosal edema, (d) production of nitric oxide, which is a vasodilator, from the maxillary sinuses, and (e) effects of vasodilating neuropeptides (73,74).

Nasal biopsy results from symptom-free gravidas showed glandular hyperactivity manifested by swollen mitochondria and increased number of secretory granules (73). Special stains demonstrated increased metabolic activity, increased phagocytosis, and increased acid mucopolysaccharides, thought to be attributed to high concentrations of estrogen. Similar findings were present in gravidas with nasal symptoms. Additional findings included increased (a) goblet cell numbers in the nasal epithelium, (b) cholinergic nerve fibers around glands and vessels, and (c) vascularity and transfer of metabolites through cell membranes (73). Regarding postnasal drainage, it has been estimated that in nonpregnant females, 700 to 900 mL of nasal secretions are generated per day for proper conditioning of inspired air. In some gravidas, this volume may be even greater, and secretions are not reabsorbed, which results in symptoms of rhinitis, postnasal drip, or cough.

Nasal congestion causing symptoms is more likely to occur in the second and third trimesters. However, it may occur in the first trimester as well (72). The differential diagnosis for rhinitis of pregnancy includes allergic rhinitis, nonallergic rhinitis (including nonallergic rhinitis with eosinophilia), nasal polyposis, and rhinosinusitis or purulent rhinitis resulting from enlarged inferior turbinates that are occlusive with the nasal septum. There can be referred pain to the sinuses consistent with rhinologic or contact headache, a condition that mimics an exacerbation of rhinosinusitis. Rhinitis medicamentosa may be present when there has been excessive use of topical decongestants.

Treatment of nasal symptoms during gestation necessitates an accurate diagnosis, effective pharmacotherapy, and, in some cases, avoidance measures.

For example, smoking and illicit drugs should be discontinued, as should topical decongestants. Intranasal budesonide, beclomethasone dipropionate, or fluticasone are indicated to relieve nasal obstruction. There are published asthma data for budesonide, beclomethasone dipropionate, and fluticasone; however, the very low bioavailability of other corticosteroids, such as mometasone and ciclesonide, suggests that they also are appropriate during gestation. If large nasal polyps are present and topical corticosteroids are ineffective, a short course of prednisone should be prescribed. The blood glucose should be monitored because the gravida is prone to hyperglycemia.

Antihistamines help gravidas with milder degrees of allergic rhinitis and occasionally with some nonallergic types of rhinitis. In a classic study published in 1977, there had been very long-term experience and safety for chlorpheniramine (1,070 exposures), diphenhydramine (595 exposures), and tripelennamine (121 exposures) (75). These first-generation antihistamines remain appropriate (Table 39.2), but second-generation antihistamines are preferable (63) and infrequently sedating. There is published experience with loratadine in pregnancy (76–78). By analogy, the metabolite of loratadine, desloratadine, should be appropriate as well. Cetirizine and its parent, hydroxyzine, were not associated with teratogenic effects in 39 and 53 pregnancies, respectively (79) or in 196 pregnancies, of which 153 women used cetirizine within 5 weeks of the last menstrual period (80). Data on cetirizine have shown that it is not teratogenic (79,80). The safety of hydroxyzine and promethazine is well established because they are treatments for hyperemesis gravidarum (81). Although administered intranasally, there is insufficient information regarding pregnancy for azelastine. Thus, this medication is not advised (63).

For perspective, the FDA classification system category B means that animal studies are negative, but that human studies have not been conducted or that animal studies are positive; but such findings of fetal risk have not been demonstrated in human pregnancies. The FDA category C implies that animal studies have identified adverse fetal effects and that there are no controlled studies in human pregnancies or human data aren't available (82). The proviso is to use such medications only if the "potential benefit outweighs the potential risk to the fetus" (82). The FDA category B medications include chlorpheniramine, loratadine, and cetirizine, whereas fexofenadine and azelastine are FDA category C (82). The leukotriene-receptor antagonists, montelukast and zafirlukast, are FDA category B (82). Intranasal (or ocular or orally inhaled) cromolyn is considered appropriate based on evidence by oral inhalation for asthma

(1,2,32,62) and is FDA category B. Except for budesonide, nasal corticosteroids remain FDA category C, although their benefits outweigh any identified risks.

The author tries not to prescribe pseudoephedrine to avoid potential α-adrenergic stimulation of uterine vessels, even though it has not been found to be teratogenic (75,82). Phenylpropanolamine (not available in the United States) in 726 exposures was associated with significantly greater risk of malformations (ear and eye), whereas this risk was not detected with pseudoephedrine (39 exposures) or phenylephrine (1,249 exposures) (75).

Antibiotics for pregnant women with infectious rhinosinusitis or purulent rhinitis are listed in Table 39.2. Ampicillin, amoxicillin, amoxicillin-clavulanate, azithromycin, and cephalosporins—all category B—are initial antibiotics, depending on the prior therapy of the gravida. Sulfonamides are contraindicated because of the possibility of G6PD deficiency in the fetus. Tetracyclines are contraindicated because of maternal fatty liver during gestation (third trimester) and staining of teeth in the infant. Human experience with clarithromycin is not available, so azithromycin should be used if it is indicated. The FDA pregnancy category C antibiotics consist of aminoglycosides, chloramphenicol, clarithromycin, quinolones, sulfonamides, tetracycline derivatives, and vancomycin.

Allergen immunotherapy (SCIT and SLIT) helps reduce the need for medications in cases of allergic rhinitis or asthma. This therapy can be continued in pregnancy, and if symptoms are severe and the gravida agrees, either immunotherapy may be initiated during gestation in my opinion. During SCIT in 121 pregnancies in 90 gravidas, 6 gravidas experienced anaphylaxis (64). No abortions or other adverse effects occurred (64). The decision to begin SCIT after delivery often is made for the purpose of convenience and ability of the woman to present for injections in a timely manner. Severe allergic rhinitis symptoms during gestation can be treated with intranasal corticosteroids and H_1 antihistamines.

As stated earlier, the dose of SCIT can be increased in the absence of large local reactions or systemic reactions. There is no evidence that the incidence of anaphylaxis from allergen immunotherapy (or skin testing) is greater during the time of gestation.

Replacement immunoglobulin for gravidas with primary or secondary immunodeficiency should be continued or initiated during gestation. The dosage is at least 0.4 to 0.6 g/kg every 4 weeks.

URTICARIA, ANGIOEDEMA, AND ANAPHYLAXIS

Urticaria or angioedema should be evaluated and treated during gestation with little change from the nongravid state, as detailed in Chapter 31. Some causes for urticaria and angioedema include foods, medications, infections (usually viral), and underlying autoimmune conditions, such as collagen vascular disorders. Some episodes of urticaria are attributable to dermatographism or other physical urticarias, chronic (idiopathic or spontaneous) urticaria, or idiopathic acute urticaria. The differential diagnosis during gestation includes hereditary angioedema (HAE) (83–91), polymorphic eruption of pregnancy (formerly known as pruritic urticarial papules and plaques of pregnancy or PUPPP) (92,93), pemphigoid gestationis (formerly known as herpes gestationis) (93), and atopic eruption of pregnancy (formerly known as prurigo of pregnancy) (93).

In the classic series of Frank et al., (87) there was an increased frequency of attacks of HAE in only 2 of 25 gestations. No acute episodes of HAE occurred during delivery. In contrast, Chappatte and de Swiet reported on the unpredictability of HAE during gestation and a maternal fatality (88). From a series of 227 pregnancies in 107 women in the PREHAEAT project of the European Union, HAE worsened in 38% of women, was unchanged in 32%, and was less severe in 30% (89). It was reported that the course of HAE was usually similar to the prepregnancy course (89). The concentration of C1 inhibitor declines in normal pregnancy because of increased plasma volume. Some gravidas have worsening clinical symptoms and create major management problems. In women with HAE, nonhormonal contraception is advisable as a rule, including avoiding estrogen–progestin patches and vaginal rings (90). Stanozolol or danazol results in a four to fivefold increase in the concentration of C1-inhibitor (C1-INH) and C4. Although stanozolol has been administered during gestation without masculinizing fetal effects or fetal loss (88), anabolic steroids are discouraged and contraindicated in gravidas with HAE (85,90). (Contraception should be used if a woman is receiving attenuated androgens for HAE.) Genetic counseling is advisable for women with HAE because it is an autosomal-dominant condition, although there is incomplete penetration.

For acute severe, central episodes of HAE, rapid administration C1-INH concentrate (plasma derived or recombinant) is indicated (85,90). The bradykinin 2 receptor antagonist, icatibant, and the kallikrein inhibitor, ecallantide, are also the available treatments (85,90). Fresh frozen plasma may be infused on an emergent basis in some situations (85,90), but there is the possibility of aggravating the episode. The basis for this statement is that in

addition to the C1-INH that is supplied, fresh frozen plasma contains factor XII, prekallikrein and high-molecular-weight kininogen that could increase the generation of bradykinin (90). In resource-poor situations, it may be necessary to administer anabolic steroids for the acute episode, in particular, danazol 600 to 800 mg immediately or stanozolol, 4 mg four times a day, and airway care measures (intubation or tracheostomy). Similarly, the antifibrinolytic drug, tranexamic acid, is not the first choice for acute management (on demand therapy) because of potential thrombotic effects. However, it has not been associated with teratogenic effects (85,90). Three pregnancies in one gravida occurred uneventfully despite use of ε-amino-caproic acid (91).

During gestation, no specific maintenance therapy is necessary in gravidas with peripheral HAE. Based on Frank's series of gravidas with peripheral or central (upper airway involvement) HAE, exacerbations during the time of tissue trauma, delivery, did not occur (87). In the PREHAEAT project, there were exacerbations of HAE postpartum or within 48 hours of delivery in just 6% of pregnancies (89,90). If an episode of upper airway obstruction occurs during a cesarean delivery, C1-INH (20 U/kg), icatibant, ecallantide, fresh frozen plasma, danazol, or stanozolol, and intubation would be indicated (90).

For long-term treatment of severe HAE during pregnancy, C1-INH replacement is preferable (1,000 U, intravenously, twice a week) (85,90). Tranexamic acid is another option but is contraindicated in women with a history of clotting. As noted, there are reports of androgens being used during gestation, but that older approach requires laboratory monitoring and patient consent. It is now considered contraindicated by an expert panel (90).

Polymorphic eruption of pregnancy (formerly known as PUPPP) occurs in the last trimester and begins on the abdomen with numerous extremely pruritic, erythematous, urticarial plaques, and papules surrounded by pale halos (92–94). Topical, moderate strength, corticosteroids are of value, and maternal or fetal complications are unlikely. A self-limited condition, the plaques and papules, may last until 6 weeks postpartum. Pemphigoid gestationis consists of intense pruritus, followed by lesions that may be bullous, papulovesicular, or pustular (94). Some gravidas develop tense grouped, herpetic-type vesicles on the abdomen or extremity. This condition is not related to current or past infections with herpes virus (94). Atopic eruption of pregnancy refers to intensely pruritic, grouped papules or pustules (but not blisters) typically on extensor surfaces of extremities (94). Excoriation is frequent. Treatment is symptomatic with moderate strength topical corticosteroids and H_1 antihistamines. The papules

may last for weeks or months after the pregnancy.

Pharmacologic treatment of chronic urticaria or angioedema often is required. The H_1 antihistamines listed in Table 39.2 are recommended. Prednisone may be indicated for acute exacerbations of urticaria, angioedema, or anaphylaxis. Leukotriene-receptor antagonists are appropriate in pregnancy but often do not provide relief.

Anaphylaxis during gestation has been described after penicillin (95), cephalosporins (96), oxytocin (97), diclofenac (98), the plant-based vitamin K, phytomenadione (99), bupivacaine (100), ferric gluconate (101), iron sucrose (102), anti-snakebite venom (103), anti-D immunoglobulin (104), latex (105), succinylcholine (106), misoprostol by tablet (107), dinoprostone by intracervical gel (108), and Hymenoptera stings (109). There are reports of exercise-induced anaphylaxis with unaffected delivery (110). Anaphylaxis during gestation has caused fetal distress, fetal encephalopathy, fetal demise, and, very rarely, maternal death. Gravidas have experienced profound shock with reduced uterine blood flow during anaphylaxis as the fundamental insult to the fetus. As in other cases of anaphylaxis, prevention and emergency medications and therapy are needed. Epinephrine intramuscularly should be administered promptly. If the gravida is hypotensive, then usual resuscitative measures should be instituted to maintain blood pressure, circulation, and the airway along with intravenous pressors, if indicated. Obstetric assistance should be obtained immediately should cesarean delivery be indicated.

VENOM IMMUNOTHERAPY

Venom immunotherapy is a highly efficacious form of therapy to prevent future episodes of Hymenoptera anaphylaxis. Graft first reported a successful pregnancy in a gravida treated with maintenance dosages of wasp and mixed vespid venoms (111). Subsequently, the Committee on Insects of the AAAAI reported 63 pregnancies in 26 gravidas with no definite systemic reactions (112). Of 43 gestations, five resulted in spontaneous abortions is thought to be unrelated to stings or immunotherapy. One term infant (2.7%) had multiple congenital cardiovascular malformations; this incidence is within the range of expected congenital malformations. In 2011, the Joint Task Force on Practice Parameters for immunotherapy of the AAAAI, ACAAI, and the Joint Council of Allergy, Asthma and Immunology stated that venom immunotherapy can be initiated during pregnancy (65). The author advises continuing the buildup during the injections in the absence of systemic reactions or large local reactions

(>8 cm). Other issues should be discussed with the gravida, such as avoidance measures and how and when to self-administer epinephrine.

◼ MATERNAL DIET

Is there a "window of opportunity" to prevent allergic conditions by modifying the diet of the gravida? There remains insufficient evidence to support restrictive (hypoallergenic) diets by the gravida as a means to prevent food allergy, asthma, and atopic dermatitis (113,114). Furthermore, it remains unproved that breastfeeding leads to a reduced risk of food allergy or asthma although it may lead to a delay in onset of atopic dermatitis (any protective benefit is lost after 18 months of age). All conditions have high heritability: peanut allergy 82% to 87%, asthma 87%, and atopic dermatitis 74% (113).

When gravidas ingested high-dose fish oil supplements beginning at week 24 of gestation, there was reduced wheezing or asthma over the first 5 years of life in their children (115). Fish oil capsules contain long-chain polyunsaturated fatty acids, eicosapentaenoic acid, and docosahexaenoic acid. The benefit was superior to the active comparator, olive oil, which contains oleic acid and linoleic acid (115). Persistent wheezing or asthma occurred in 16.9% of children whose mothers received the high-dose long-chain polyunsaturated fatty acids compared with 23.7% in children whose mothers were given olive oil supplements (115). Most of the benefit was attributable to children whose mothers had low, preintervention blood concentrations of the fatty acids. There was a reduction in the number of episodes of pneumonia and bronchiolitis but not in the risk of eczema or allergic sensitization. It is not known whether fish oil supplementation in the third trimester will become a widespread recommendation for prevention of persistent wheezing or asthma.

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Eosinophilic Esophagitis

NIRMALA GONSALVES, IKUO HIRANO, AND ANNE M. DITTO

■ EPIDEMIOLOGY AND DEMOGRAPHIC CHARACTERISTICS

Over the past several years, eosinophilic esophagitis (EoE) has become increasingly recognized as an important disease by allergists, internists, and gastroenterologists caring for both pediatric and adult patients. Although prior studies have abbreviated this entity as EE, the new guidelines have adopted the abbreviation "EoE" to distinguish eosinophilic esophagitis from erosive esophagitis, which gastroenterologists refer to as EE (1). EoE may occur in isolation or in conjunction with eosinophilic gastroenteritis. Eosinophilic gastroenteritis refers to group of conditions involving eosinophilic infiltration of other gastrointestinal organs, such as the stomach, intestine, or colon. This chapter focuses solely on EoE.

Previously considered a rare condition, there has been a dramatic increase in reports of EoE from North and South America, Europe, Asia, Australia, and the Middle East. There have yet to be cases identified in the African continent. The cause for this rise is multifactorial, including a true increasing incidence of EoE in addition to a growing awareness of the condition among gastroenterologists, allergists, and pathologists (2,3). Noel et al. suggest that the incidence of EoE has been rising in a population of children residing in Hamilton, Ohio. In 2000, the authors estimated the incidence to be 0.91 per 10,000 with a prevalence of 1 per 10,000 compared to 1.7 in 10,000 and a prevalence of 10.4 in 10,000 in 2007 (4). Straumann and Simon studied a population of adults in Olten County, Switzerland, and found a similar trend. They estimated an incidence of 0.15 cases per 10,000 adult inhabitants with a prevalence of 3 per 10,000 inhabitants of their catchment area in Switzerland (5). These numbers are likely to underestimate the true incidence and prevalence of EoE in the general population because these data are based on patients with symptoms sufficient to warrant endoscopy. A population-based study in Sweden randomly surveyed 3,000 adult members of the population, and 1,000 healthy adults underwent endoscopy with esophageal biopsies. This group found that histologic eosinophilia meeting their

criteria for definite and probable EoE was present in 1% of the population (6). These numbers suggest that incidence of EoE may 1 day approximate that of other immunologically driven disorders, such as inflammatory bowel disease. In addition, increasing publications about EoE in the past several years are contributing to the awareness of this condition in both the gastroenterology and pathology community (7). For instance, a PubMed search of articles using the term *eosinophilic esophagitis* resulted in 1,829 publications from 2000 to November 2016 compared to only 38 publications prior to this time.

EoE has a male predilection. Results from 323 adult patients from 13 studies observed that 76% were males with a mean age of 38 years (range 14 to 89 years). Results from 754 pediatric patients from 16 studies found that 66% were male with a mean age of 8.6 years (range 0.5 to 21.1 years) (8,9). EoE has been described in patients with varied ethnicities, including those of Caucasian, African American, Latin-American, and Asian descent (9). One pediatric review suggested that there was a racial predilection with 94% of the patients being Caucasian; however, more recent studies have suggested rising cases in the African American population (10). A familial pattern has been recognized in the pediatric population. In a case series of 381 children with EoE, 5% of patients had siblings with EoE and 7% had a parent with either an esophageal stricture or a known diagnosis of EoE (11). One study showed that eotaxin-3, a gene encoding an eosinophil-specific chemoattractant, was the most highly induced gene in pediatric EoE patients (12). This finding supports the previous reports suggesting a potential genetic predisposition to EoE, and several case reports also suggest familial clustering of this condition in adults; therefore, a workup of patients should include a thorough family history (13,14).

CLINICAL FEATURES

As with other diseases, some age-related differences in clinical presentation are noted between children and adults (15,16). The most common presenting symptoms in adults include dysphagia, food impaction, heartburn, and chest pain (1). In one study, as many as 50% of adults presenting with food impaction were ultimately diagnosed with EoE.

In children, the most common presenting symptoms include vomiting, heartburn, regurgitation, emesis, and abdominal pain (11,17). While younger children rarely present with dysphagia and food impaction, these presentations were more commonly seen in older children and adolescents (4). In adults, this diagnosis has often been overlooked, and many patients have had endoscopies

with alternate diagnoses, including Schatzki rings or gastroesophageal reflux disease (GERD) prior to a diagnosis of EoE (18). In many cases, these patients had undergone repeated endoscopies, esophageal dilations, and a delay in the institution of appropriate medical therapy. In previous years, the presence of eosinophils in esophageal mucosal biopsies was equated with GERD, and therefore, some specimens may have been classified as reflux. Owing to this potential overlap, gastroenterologists who suspect a diagnosis of EoE should specifically request tissue eosinophil counts by the pathologist to help differentiate this diagnosis from GERD.

Endoscopic Findings

The most common endoscopic features in adults with EoE include linear or longitudinal furrows (80%), mucosal rings (64%), small caliber esophagus (28%), white plaques and/or exudates (16%), and strictures (12%) (19) (Fig. 40.1). In a large clinical series of 381 children, the most common endoscopic features were linear furrows (41%), normal appearance (32%), esophageal rings (12%), and white plaques (15%) (11,17). It is important to note that the classic endoscopic features may be subtle and missed during endoscopy. Therefore, it is suggested that biopsies be taken for the clinical indication of unexplained dysphagia, refractory heartburn, or chest pain despite normal endoscopic findings. A new endoscopic reference scoring tool called EREFS has been developed and validated and is a helpful tool to objectively characterize endoscopic abnormalities (20).

Histologic Features

While certain endoscopic features are characteristic of EoE, this condition is ultimately diagnosed by obtaining biopsy specimens that demonstrate histologic findings of increased intramucosal eosinophils in the esophagus without concomitant eosinophilic infiltration in the stomach or duodenum (9) (Fig. 40.2). Other histologic features of this condition include superficial layering of the eosinophils, eosinophilic microabscesses (clusters of ≥4 eosinophils), intercellular edema, and degranulation of eosinophils. Other inflammatory cells, such as lymphocytes, polymorphonuclear leukocytes, and mast cells, may be present in the epithelium (21). Another histologic finding in EoE is epithelial hyperplasia, defined by papillary height elongation and basal zone proliferation. Epithelial hyperplasia is also a cardinal feature of the histopathology of reflux esophagitis. Studies have also shown the presence of subepithelial fibrosis in biopsies of adults and children with EoE, suggesting that deeper layers of the

esophagus may be involved (22). Involvement of deeper layers of the esophagus has further been supported by the use of endoscopic ultrasound (23). It is speculated that this mucosal and submucosal fibrosis may lead to esophageal remodeling and decreased compliance of the esophagus, thus contributing to the symptoms of dysphagia even in the absence of an identifiable stricture.

Although a single diagnostic threshold of eosinophil density has not been determined, a recent consensus statement suggests using a threshold value of ≥ 15 eosinophils per high-power field (hpf) to diagnose EoE (1,9). It has also been demonstrated that the eosinophilic infiltration of the esophagus may not be evenly distributed within the esophagus (18). Therefore, it is suggested that biopsies be obtained from both the proximal and distal esophagus to obtain a higher diagnostic yield and perhaps increase the specificity of the diagnosis. A retrospective study of adult EoE patients found that obtaining more than five biopsies maximizes the sensitivity based on a diagnostic threshold of ≥ 15 eos/hpf in the adult population (18). A follow-up study using a pediatric cohort demonstrated that three biopsies yielded a diagnosis of EoE in 97% of patients (24). In both the adult and pediatric studies, biopsies taken of only the proximal or distal esophagus missed the diagnosis in up to 20% of cases, emphasizing the importance of taking biopsies from different locations. While current guidelines are using an absolute threshold of 15 eos/hpf to determine active inflammation, development of newer histologic scoring tools may have better accuracy in assessing disease activity (21,25).
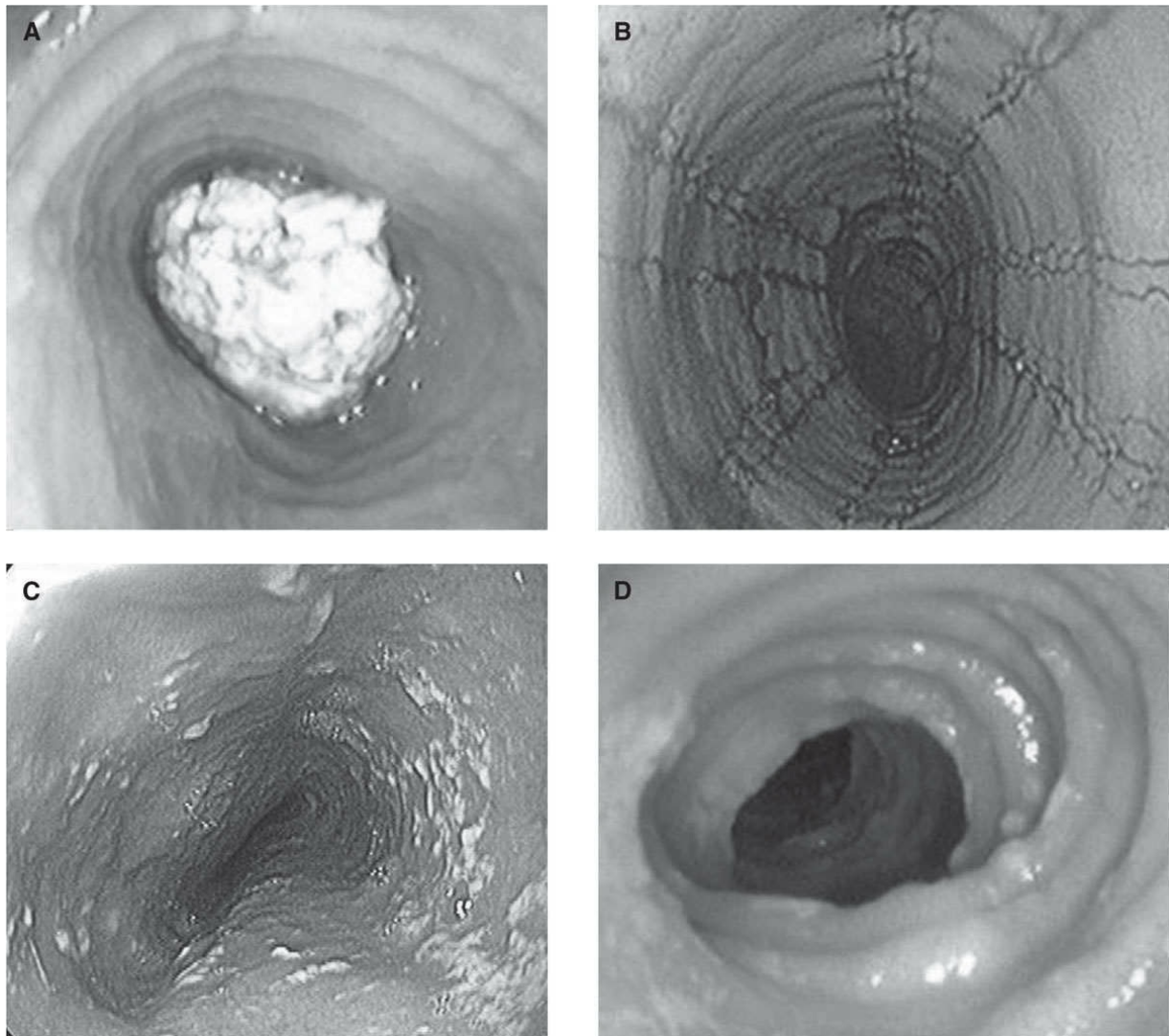
■ **FIGURE 40.1** Endoscopic photographs showing common features of eosinophilic esophagitis. **A:** Concentric mucosal rings seen throughout the length of the esophagus in a patient presenting with a food impaction. **B:** Linear furrows or creases in the esophageal mucosa. **C:** White exudates/plaques, which correspond to areas of eosinophilic abscess eruption through the esophageal mucosa. **D:** Concentric mucosal rings and small caliber esophagus. (Endoscopic photos courtesy of N. Gonsalves, MD, and I. Hirano, MD.)

Diagnostic Criteria

Recent consensus recommendations based on a systematic review of the literature and expert opinion have led to the following diagnostic criteria. EoE is a clinicopathologic disease characterized by (a) the presence of symptoms including but not limited to dysphagia and food impaction in adults and feeding intolerance and GERD symptoms in children, (b) eosinophil predominant inflammation of ≥15 eos/hpf in the esophageal tissue, and (c) eosinophilia

isolated to the esophagus after an adequate high-dose proton pump inhibitor (PPI) trial, (d) exclusion of other disorders associated with similar clinical, histologic, or endoscopic features.

Proton Pump Inhibitor-Responsive Esophageal Eosinophilia

Patients with clinical and histologic features compatible with EoE but who respond histologically to a PPI have been described as having PPI-responsive esophageal eosinophilia (PPI-REE) (26,27). Although there are significant overlapping features of patients with EoE and PPI-REE, at the present time, this is considered a distinct entity from EoE (28). In a study that evaluated differences in major basic protein, tryptase, and eotaxin-3 levels in patients with PPI-REE, EoE and controls, there were significant differences in protein levels when patients with EoE were compared with controls but not with patients with PPI-REE (29). In another study, clinical and endoscopic features of patients with PPI-REE were indistinguishable from patients with EoE (30). The mechanisms by which PPIs improve esophageal eosinophilia have been shown to be independent of acid suppression and rather on effect of blocking eotaxin-3 and its esophageal epithelial eosinophil effect (31).
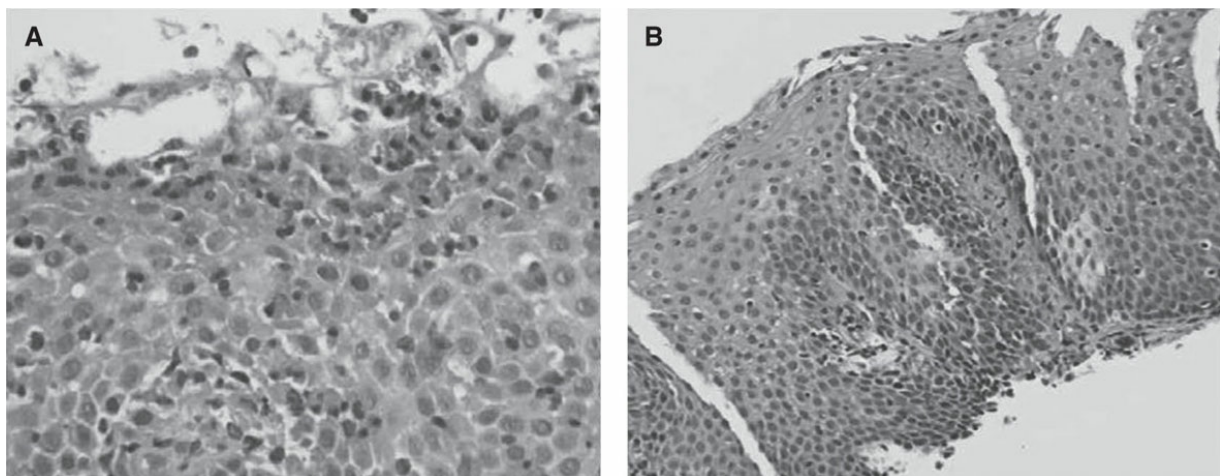
■ **FIGURE 40.2** Common histologic appearance in eosinophilic esophagitis (EoE). *A*: Demonstrates superficial layering of eosinophils in the esophageal mucosa with the presence of microabscesses seen in most patients with EoE (×400). *B*: Demonstrates the epithelial hyperplasia seen in EoE (×200). (Histologic photographs courtesy of N. Gonsalves, MD.)

Additional Diagnostic Testing

Intraesophageal pH Testing

The role of intraesophageal pH testing in EoE is not clearly defined as patients

with response to a course of PPI therapy despite normal pH testing (32).

Radiography

Radiologic studies, such as barium esophagrams, may be used in the workup of patients with EoE but are sometimes nondiagnostic. A recent study that correlated endoscopic and radiologic features in EoE demonstrated that both esophageal strictures and esophageal rings may be identified on barium studies of patients with EoE (33). In addition to identifying a stricture, the use of upper gastrointestinal contrast studies may better characterize the length of a stricture as well as its caliber. This information may be helpful prior to subsequent upper endoscopy by alerting the endoscopist to use a smaller caliber endoscope or to proceed more cautiously with passage of the endoscope.

Manometry

Esophageal manometry has been previously studied in patients with EoE. The most common abnormality noted was elevation in peristaltic velocity. Some patients had also failed esophageal peristalsis, repetitive simultaneous esophageal contractions, and impaired relaxation of the lower esophageal sphincter. Such manometric abnormalities may provide an explanation for the symptoms of dysphagia that occur in patients without a discernable esophageal stricture. Manometry is not typically used in workup of patients with EoE because of nonspecific findings; however, it may be helpful in patients who have persistent dysphagia without clear endoscopic abnormalities.

Functional Luminal Impedance Planimetry

Functional luminal impedance planimetry is a newer technique that has been studied to measure esophageal pressures and distensibility (34,35). Although it is still considered an investigational tool, findings have suggested that patients with EoE have less esophageal compliance compared to patients with reflux or controls and that patients with esophageal diameters <16 mm have a higher risk of food impactions (35).

PATHOGENESIS

Data from both human and murine studies are consistent with EoE being an allergic disorder with a T_H2 cytokine profile typical of allergic disease (36,37), and the increase in incidence of EoE mirrors the increase in allergic diseases over the past few decades (38). A link has been shown between EoE and atopy and among patients with EoE in that there is a high incidence of atopic disease, such as allergic rhinitis (AR), atopic dermatitis, and asthma (17). In addition,

there is a prominent presence of eosinophils as well as pathologic findings that share similarity with other allergic diseases such as asthma, for example, thickened mucosa and basal layer hyperplasia. T_H2 lymphocytes are demonstrated in the esophageal mucosa (37) and play an essential role in EoE as T-cell–deficient mice, but not B-cell deficient, are protected from developing allergen-induced EoE. T_H2 lymphocytes are stimulated to secrete T_H2 cytokines in an antigen-specific manner, with both food and aeroallergens likely playing a role. Interleukin (IL)-4, IL-5, and IL-13 have been shown to be upregulated in EoE and correlate with disease activity (39), with IL-5-induced tissue-specific eosinophilia causing remodeling (40,41), as well as reversibility of IL-13 induction with glucocorticoids. Transforming growth factor β (TGF-β) from both mast cells and eosinophils contributes to remodeling (42) and has been shown to play a role in smooth muscle contraction, possibly contributing to esophageal dysmotility seen in EoE (43). Kirsch et al. (44) demonstrated increased numbers of mast cells and activation of mucosal mast cells, distinguishing EoE from GERD. There is marked upregulation of eotaxin-3 gene expression in patients with EoE as well as interaction between eotaxin-3 and its receptor CCR3 in EoE (45). Furthermore, peripheral blood eosinophils with CCR3 expression and increased tissue $CD4^+$ cells expressing IL-5 have been demonstrated. These correlate with eosinophils in the esophagus and also with disease activity, being lower in patients whose disease is in remission (46). The epithelium is shown to play a role in EoE, both by loss of barrier protection and by directly promoting inflammation through cytokine release. Desmoglein-1 levels are decreased in epithelial biopsies of EoE patients. This decreased in barrier function, mediated by IL-13, may allow allergen penetration, thereby leading to sensitization (47). Filaggrin (FLG) levels are decreased as well, and this is reversed with improvement in barrier function in patients treated with steroids (48). Invariant natural killer T cells are increased in the esophagus of children with EoE. In response to sphingolipids found in milk, these cells are activated to produce T_H2 cytokines (49). Markers for these cells are decreased with dietary elimination in children younger than 6 years of age. Group 2 innate lymphoid cells (ILC2s) may also be a source of T_H2 cytokines IL-5 and IL-13, possibly mediating signaling from epithelial cells. ILC2s are found to be upregulated in esophageal tissue of patients with active EoE (50), distinguishing this from inactive EoE, PPI-REE, or GERD.

Genetic studies have provided additional insight into the pathogenesis of EoE. A study of families of EoE probands showed a relative risk ratio 10- to 64-fold greater than the general public, with the higher risk seen in male siblings. Yet

results from twin studies showed that environmental factors play a much greater role, responsible for 81% of the phenotypic variance with heredity explaining only 15% (51).

A specific EoE "transcriptome" has been found through gene expression profiling of biopsy specimens obtained from EoE patients. This "transcriptome" demonstrates 574 altered gene expressions, with eotaxin-3 being the most highly induced gene, and distinguishes EoE from healthy controls and patients with chronic esophagitis (52). This transcriptome correlates with esophageal eosinophil levels, and thus 98% of it normalizes with glucocorticoid treatment (12). Genome-wide associations studies on pediatric EoE show significance at one locus on chromosome 5q22, a region that codes for thymic stromal lymphopoietin (TSLP) (53) as well as an association at four loci: *c11orf30*, *STAT6*, ANKRD27, and chr2p23.1 which includes the *CAPN14* gene, the latter two of which are unique to EoE. TSLP is shown to be upregulated in biopsies of EoE patients and, through its basophil stimulation, is reported to be crucial for the development of EoE (54). Through candidate gene analysis, a high association with CCL26 gene (gene for eotaxin-3) and disease risk has been reported (52), and this association is independent of atopy. In addition, a loss of function single-nucleotide polymorphism (SNP) in *FLG* (2282de14) associates with EoE risk, independent of atopy as well as SNPs in the gene for TSLP. EoE more resistant to treatment is associated with an SNP in the TGFβ1 region (43).

Allergens

EoE, with its T_H2 cytokine profile, is thought to be allergic, yet the allergen remains elusive. Food is thought to play a role in both children and adults, yet the role it plays may be somewhat different in these two age groups. The concept of food as the allergenic cause was first introduced by Kelly et al. (55) who described 10 children with severe GERD symptoms unresponsive to PPI therapy. Eight patients had resolution and two had improvement in symptoms when placed on an elemental diet (ELED) for 6 weeks (Neocate One+, SHS North America, Gaithersburg, MD; EleCare, Ross Pediatrics, Abbott Laboratories, Abbott Park, IL). Histologically, patients improved as well; eosinophil numbers decreased from a median of 41 per hpf (range 15 to 100) to a median of 0.5 eos/hpf (range 0 to 22). The demonstration of recurrent symptoms on food reintroduction added credence to the role of food allergy. Markowitz et al. (56) showed similar results in a study of 51 children diagnosed with EoE, using strict criteria to rule out GERD (56). For 3 months, 346 children with symptoms of GERD were treated with a PPI. Those who clinically responded to empiric PPI

therapy or demonstrated an abnormal 24-hour pH study after treatment were excluded from the study. The remaining 51 children were treated with an ELED for 4 weeks with marked response. Eosinophil counts per hpf decreased on average from 34 to 1. Symptoms recurred with reintroduction of food. Similar results have been reproduced in several studies in children from multiple centers with larger cohorts showing resolution of symptoms and histologic evidence of EoE (57,58). However, ELEDs are unpalatable and very difficult to maintain and oftentimes require tube feedings. In the study by Liacouras et al., 80% of the children were fed by nasogastric tube, and eight patients were unable to tolerate the diet. This poor tolerability has led to trials of empiric and allergy testing-directed food elimination. Investigators retrospectively studied children with EoE, comparing those treated with an ELED to those treated with a diet eliminating the eight (six) most common food groups involved in allergy: nuts (tree nuts and peanuts), seafood (fish and shellfish), wheat, soy, milk, and eggs. This empiric approach was termed the six food elimination diet (SFED) (57). There were 60 children studied, 35 on SFED and 25 on ELED. In all, 25 of the 35 patients (69%) on SFED and 22 of 25 (88%) on ELED showed improvement in symptoms and resultant eosinophil counts ≤10 per hpf.

Work has been done to try to identify culprit foods for more directed rather than empiric food elimination. However, identification of the food with traditional methods of testing for food allergy has had limited success. While immunoglobulin E (IgE) is thought to play a role, its exact role is not clear. Most patients are sensitized to food or aeroallergens or both, as demonstrated by positive skin-prick tests (SPTs) or specific IgE (sIgE) (48). In addition, local IgE production in the esophagus has been demonstrated. However, EoE patients do not have reactions that are typical of IgE-mediated food allergic reactions such as urticaria or anaphylaxis, and because reactions may not be immediate, it has been difficult to identify responsible foods by history. In addition, trials using omalizumab, a monoclonal anti-IgE antibody for the treatment of EoE showed little success. Moreover, studies show that symptoms do not necessarily correlate with disease (59). Children, however, tend to have more immediate symptoms such as vomiting, and it is possible that their histories and allergy test results may be more reliable. Traditional tests used for determining food allergy, SPT and enzyme-linked immunosorbent assay Immuno-CAP, are used to detect IgE antibodies and, therefore, may have a limited role in predicting food allergens in EoE, particularly in adults (60). Furthermore, the sensitivity, specificity, as well as positive and negative predictive values for these tests have shown substantial variability.

Mechanisms other than an IgE-mediated food allergy may be involved in the pathogenesis of EoE, such as a T-cell–mediated delayed response (61). Spergel et al. (58) have attempted to identify potential food allergens by combining allergy patch testing (APT) and SPT for foods modeled after testing used in atopic dermatitis (58). One hundred forty-six children diagnosed with EoE were placed on diets eliminating foods identified by APT and SPT for 4 to 8 weeks. Foods tested were based on history. Of the 146 in the study, 112 children (77%) improved, achieving a mean of 1.1 eos/hpf. Of these 112, 40 were placed on ELED because of nutritional deficiencies that resulted from the dietary restriction. On average, five foods were eliminated. SPT identified 3.2 ± 4.3 foods with egg, milk, soy, peanut, chicken, wheat, and beef being the most common. APT identified 3.1 ± 2.6 foods with corn, soy, wheat, milk, rice, chicken, beef, and potato being most common. The causative foods were identified by elimination of a single food in 18 patients and by reintroduction of foods in 21 patients (58). Based on a cohort of children in whom the causative food could be identified, Spergel et al. demonstrated that adding APT to SPT increases both sensitivity and specificity for most foods, with the exception of milk, which had poor sensitivity and specificity for both. On average, using both testing methods identified one additional food.

Other than for atopic dermatitis, the use of APT in evaluating food allergy remains controversial (62,63). There is no standard determined for the food preparation used (63). Finn chamber size has been shown to be critical in the interpretation of the results (64,65). Studies to standardize test interpretation are ongoing (62). In children, foods chosen for testing are based on symptoms (57,58). However, in adults, whose symptoms differ, it is typically difficult to identify potential food triggers.

Food elimination, although successful in adults, the response is not as pronounced as seen with children (66). Gonsalves et al., following the same protocol used in the aforementioned pediatric study, applied the SFED in 50 adults for 6 weeks. Median peak eos/hpf pre- and post-SFED were 34 and 8 in proximal and 44 and 13 in distal biopsies, respectively ($P < 0.05$). There was histologic improvement in the majority of patients with 64% of patients having a peak <5 eos/hpf and 70% <10 per hpf. Symptoms improved in 94% of patients. Endoscopic features of rings, furrows, and exudates showed improvement. Reintroduction of foods was completed systematically in 20 patients who responded to the SFED. In all patients, the trigger food was identified, most commonly milk and wheat (66). Elemental formula, which eliminates all possible allergens, has the highest success rate for both pediatric in adult groups.

Yet differences in response still remain. In particular, adults did not have as significant improvement in symptoms, and while children had improvement in subepithelial fibrosis, adults did not show the same improvement in strictures or narrowing, other markers of remodeling (67).

Combining skin test and patch test in children is reported to be fairly sensitive and specific (68); this is not the case, however, with adults (60). In the aforementioned study by Gonsalves et al., (66) SPT correctly identified only 13% of foods that were found during reintroduction. This suggests that further studies need to be pursued to better delineate the role of allergy testing for foods in adults with EoE. Supporting this, Simon et al. (69) published a study in which six adults who were SPT or radioallergosorbent test positive to grass, rye, and wheat, eliminated rye and wheat for 6 weeks. Only one patient had improvement in symptoms, whereas none of the patients demonstrated histologic improvement. These patients were not allergic to other foods commonly considered responsible in EoE, such as egg and milk. These authors conclude that foods may not be the allergens responsible for EoE in adults and that the positive skin tests to wheat and rye in these individuals may be because of cross-reactivity with the grass aeroallergens. These studies call into question the utility of allergy testing-directed elimination diets in adult patients with EoE that rely on IgE reactivity.

Based primarily on data from adult patients with EoE, aeroallergens are candidate allergens in the pathogenesis of EoE. Sensitization to aeroallergens is more common in adults with EoE as compared to children (70). In addition, in adults, aeroallergen sensitivity predates EoE (69,71). In a study analyzing children and adults with EoE, Sugnanam et al. (70) noted that age correlated positively with aeroallergen sensitivity as determined by SPT although there was a negative correlation between age and food sensitivity. Fogg et al. (72) reported increased eosinophils in the esophagus of a patient during pollen season, with resolution out of the season, and house dust mite–specific immunotherapy was shown to improve symptoms in a child with house dust mite sensitization and difficult to treat EoE (73). In a retrospective study of 234 children, EoE was diagnosed less often in the winter months. Although eosinophil levels in the esophagus were elevated year round, they were higher in the summer and fall months (74). Others have noted eosinophilia in the esophagus of patients with AR who did not have EoE (75). A recent case series of 23 adults confirms polysensitization to aeroallergens. The food sIgE profile in these patients suggests that aeroallergens may play a role in sensitization to at least some of the foods (76).

A recent case series by Mahdavinia et al. (77) supports the theory that aeroallergens may play a role. A retrospective chart review of 186 patients with EoE from two centers, and a control group of 206 patients with AR, showed that EoE patients were more likely to be pollen allergic 155 (82.4%) versus 146 (69.9%) (P ≤ 0.001). More striking is that oral allergy syndrome (OAS) occurred much more frequently in the EoE group 79 (50.9%) versus the AR group 15 (10.2%) (P ≤ 0.001) pollen allergic groups. Of note, 100% of the AR group had nasal symptoms, whereas only 56.4% of the EoE patients had nasal symptoms. Thus, it may be that, in at least some adults, the food allergen is a protein that cross reacts to the pollen proteins to which patients first become sensitized-a progression, if you will, of the atopic march. Van Rhijn et al. (78) showed that of 76 adults with EoE, 30 were sensitized to Bet v 1 (the major allergen in birch tree) and cross-reactive foods (78). In a study of 35 adult patients with EoE, Simon et al. (79) found 43% were sensitized to *Candida albicans*, 80% to aeroallergens, and whereas only 22% demonstrated sIgE to food allergens, 69% were reactive to cross-reactive pollen allergens, most commonly profilins. In addition, dysphagia with rice and bread correlated with sensitivity to profilins, lipid transfer proteins and pathogen response (PR) proteins, most notably PR-10, whereas dysphagia with meat rarely correlated with sensitivity to meat protein. It is interesting that several studies show a seasonal increase of EoE in the summer months because this may correspond to grass season (80,81). Cross-reactive proteins shared between food and grasses are profilins.

Lack of detection of foods by SPT supports cross-reactive foods playing a role in EoE because these foods are notoriously skin test negative with commercial extracts, being positive only with fresh food-prick testing as described with the first cases of OAS (82). Indeed, skin testing to fresh foods is reported to have a higher positive rate than testing with commercial extracts in EoE patients (60). Component resolved diagnostics can identify cross-reactive foods and may serve better in testing patients with EoE.

A causative role for aeroallergen sensitivity in EoE has also been demonstrated in an animal model. Mishra et al. (83) noted eosinophils in both the lungs and esophagus in mice sensitized to aspergillus when they were then challenged intranasally with aspergillus. Aeroallergens may induce EoE via a systemic rather than local response. Nasal exposure to aeroallergens may lead to EoE just as nasal exposure has been shown to cause upregulation of activated eosinophils from the bone marrow (84–87) and deposition in the lungs (88). This may be a continuation of the "one airway" or "united airway." On the other hand, aeroallergens may act locally after being swallowed, directly causing

allergic inflammation in the esophagus. Swallowed foods that share proteins with aeroallergens may affect the esophagus just as the oral mucosa can be involved in OAS, also called pollen food allergy syndrome (89–92). A meta-analysis of oral immunotherapy (OIT) found that de novo EoE occurred in about 2.7% of patients receiving OIT (93).

■ TREATMENT

The goal of therapy of EoE is not only amelioration of presenting signs and symptoms but also prevention of disease progression and complications. In this regard, understanding the natural history of EoE is of great importance. Unfortunately, limited data exists regarding the course of untreated disease creating a challenge in managing patients, particularly those who are minimally symptomatic or even asymptomatic. As a relatively recently recognized disease, most patients with EoE have been followed for short periods of time. In the longest published study to date, Straumann and Simon followed 30 adults patients for an average of 7.2 years in the absence of medical or diet therapy (94). All patients maintained a stable nutritional state, but 97% continued to experience dysphagia. Dysphagia increased in 23%, was stable in 37%, and improved in 37%. Similarly, the degree of esophageal eosinophilia persisted but demonstrated an overall decline in most patients during the follow-up period. Although one-third of the cohort had received esophageal dilation that likely affected the dysphagia outcomes, dilation does not affect the esophageal eosinophilia. Retrospective data has associated the duration of disease with increased prevalence of esophageal stricture formation (95). This observation suggests that earlier identification and treatment of EoE may prevent progression to fibrostenosis.

Children, like adults, may be at risk for progression to fibrostenotic complications of EoE, but few long-term pediatric studies have examined the consequences of ongoing esophageal eosinophilic inflammation. Assa'ad and colleagues (17) studied a group of 89 pediatric patients over a period of 8 years and found the disease to be both chronic and relapsing. Of the patients who had resolution of their EoE with therapy, 79% later relapsed with a mean follow-up of 1.4 years. A nested, case–control study surveyed 42 pediatric patients with "retrospectively diagnosed EoE" based on review of previously collected biopsies (96). The study found that increased esophageal eosinophilia and atopy in childhood increased the prevalence of dysphagia in these patients as young adults.

THERAPEUTIC ENDPOINTS

Patients with EoE are treated for many reasons, including resolution of symptoms, improvement in quality of life, and prevention of future complications (97). The primary endpoints reported in clinical trials currently focus on symptoms and esophageal eosinophilia. Caution is needed in the interpretation of symptom improvement as a primary indicator of disease activity for both clinical practice and trials. Many patients modify or avoid ingestion of foods that are difficult to swallow. Others consciously and subconsciously develop coping strategies to facilitate swallowing, such as more careful mastication, increased liquids with solid foods, and prolonged meal times. In addition, patients may have sporadic symptoms that may not manifest during a short-term assessment period.

Histologic response is most commonly defined by a reduction in tissue eosinophilia. However, the optimal degree of reduction is poorly defined such that a variety of endpoints have been used, including thresholds of <15, <10, <6, and <5 eos/hpf. The calculation of peak eosinophil counts can be based on sampling of multiple levels of the esophagus or the mean of multiple hpfs showing the greatest density of eosinophils. Additional studies have reported endpoints based on a percentage reduction in eosinophilia (i.e., >50%, >90%) or mean eosinophil densities for a cohort. Overlooked markers, such as expression of eosinophil activation products, basal cell hyperplasia, spongiosis, subepithelial fibrosis, lymphocytes, or mast cell infiltration, may be as relevant as the actual number of eosinophils. The recent development of an EoE Histologic Severity Score has included several of these additional pathologic parameters to provide a more comprehensive and hopefully more accurate characterization of mucosal inflammation in EoE for clinical trials (21). On the other hand, histologic improvement of mucosal inflammation could be misleading as an indicator of overall disease activity. Studies have demonstrated that esophageal eosinophilia can extend to involve the submucosa as well as muscularis layers that are not sampled by esophageal mucosal biopsies (98). Pediatric and adult studies in EoE utilizing endoscopic ultrasonography revealed significant expansion of the esophageal wall and the individual layers, including the mucosa, submucosa, and muscularis propria, compared to healthy controls (99).

Medical Therapy

Proton Pump Inhibitors

The controversy surrounding the differentiation of GERD from EoE is better appreciated given the historic context, whereby esophageal eosinophilia was initially equated with GERD (100). Early adult series posited "allergic" EoE as distinct from GERD. Substantial overlap in the clinical presentation of the two entities in children, however, is more difficult to tease apart than in adults. A histologic response to PPI therapy was proposed as a diagnostic means to distinguish esophageal eosinophilia related to acid from allergic mechanisms. Recent descriptions, however, demonstrated that 25% to 50% of pediatric and adult patients with symptomatic, endoscopic, and histologic findings of EoE that resolved with PPI therapy created both surprise and confusion (101). Studies now indicate that patients with PPI-REE more closely resemble EoE than GERD from a clinical, genetic, and immunologic perspective. The benefits of PPI therapy in EoE may be because of repair of mucosal permeability defects or direct anti-inflammatory effects. Emerging views suggest that the lack of responsiveness to PPI therapy should not be utilized as a diagnostic tool to rule out GERD (102). Instead, PPI therapy can be viewed as an effective, safe, and practical initial step in the management of patients with esophageal eosinophilia. Ongoing studies elucidating the mechanism behind PPI-REE will improve our understanding and management of EoE.

Dosing and duration of PPI therapy in patients with esophageal eosinophilia has been varied. Recommended "high-dose" PPI therapy has consisted of standard dosing given twice a day (BID) or double dosing given once a day, usually for a period of 2 months (i.e., omeprazole 20 mg BID or 40 mg every day [QD] or equivalent). The majority patients responsive to high-dose PPI therapy maintain histologic response with reduction to standard dosing although case reports have described patients who lose response to PPI with prolonged use (103). Current data has not accounted for differences in dosing regimens based on variations in potency and pharmacokinetics of the different PPI formulations or genetic variation in PPI metabolism.

Topical Corticosteroids

Swallowed, aerosolized fluticasone propionate was first reported to be a successful treatment for EoE in 1998 by Faubion in a series of four children (104). Symptom resolution as well as significant reduction in eosinophils and CD3, CD8, and CD1a lymphocytes in 11 children was later demonstrated by Teitelbaum et al. (105). Subsequently, prospective adult studies extending these early reports and documented symptomatic, endoscopic, and histologic improvement in EoE with swallowed fluticasone (106). Fluticasone has

continued to be a desirable option in both children and adults because of the low systemic bioavailability owing to first-pass hepatic metabolism. To address concerns regarding esophageal delivery of the aerosol using a metered-dose inhaler system, a recent study reported effectiveness of directly swallowing the powder packets contained within the diskus formulation of fluticasone (101). Both liquid and tablet formulations of topical steroids are currently being studied in ongoing pharmaceutic trials.

The effectiveness of fluticasone in initial studies has been substantiated in randomized controlled trials. Konikoff et al. (107) conducted the first randomized, placebo controlled trial in 36 children with EoE. Fluticasone (880 µg/day) administered for 3 months induced histologic remission defined by peak eosinophil counts of ≤1 eos/hpf in 50% of patients compared with 9% in the placebo arm. Higher pretreatment esophageal eosinophilia did not predict poor responsiveness to fluticasone. Nonallergic individuals had a better response than did allergic individuals. Of note, the allergic individuals had failed or refused dietary elimination prior to study entry. Fluticasone responders were significantly younger, shorter, and weighed less than nonresponders. Alexander and colleagues conducted the first randomized placebo controlled trial of fluticasone in adults (108). Forty-two subjects were randomized to fluticasone 880 µg BID via inhaler for 6 weeks, demonstrating a 90% reduction in esophageal eosinophilia in 62% compared with none of the placebo subjects. Symptom improvement measured by the Mayo Dysphagia Questionnaire was not significant. A recent multicenter study randomized 42 patients between 3 and 30 years of age to receive fluticasone via inhaler for 3 months (109). Complete response defined by ≤1 eos/hpf was found in 65% with active drug and none with placebo. Partial response defined by <15 eos/hpf was found in 77% with active drug and 8% with placebo. Seventy-three percent of patients with complete response maintained response on a lower dose of 880 µg QD for an additional 3 months. Patients without initial complete response did not show improvement with an additional 3 months of therapy. Unlike the previous pediatric study, age, gender, anthropomorphic features, and atopic status were not associated with treatment response.

Another topical steroid that has been described is budesonide suspension. The puff and swallow technique may be difficult for some adults and younger children. A randomized, double-blind, placebo controlled trial was conducted in 36 adults with EoE (110). Budesonide 1 mg BID was swallowed during nebulized administration, resulting in a reduction in tissue eosinophilia from 62 eos/hpf at baseline to 4 eos/hpf after 15 days of therapy with no change after

placebo. Symptoms measured with a nonvalidated assessment tool improved in 84% with budesonide and 33% with placebo. Mast cell infiltration, tryptase, and CD3 staining improved after treatment. Aceves and Dohil first described the novel formulation of liquid budesonide mixed with sucralose to create a viscous suspension in a retrospective series of 20 children with EoE (42). In a subsequent randomized controlled trial of 24 children with EoE, the same authors demonstrated an 87% histologic response (≤6 eos/hpf) following 12 weeks of oral viscous budesonide (1 to 2 mg QD) (111). Symptom and endoscopic features also significantly improved. A novel formulation of budesonide in a liquid oral suspension dosed at 2 mg BID for 12 weeks was examined in a recent randomized, double-blind, placebo controlled, multicenter trial in 93 patients with EoE between 11 and 40 years of age. The study was the first to meet a co-primary endpoint of histologic improvement defined by <6 eos/hpf (39% with budesonide compared with 3% with placebo) and symptom response defined by a validated, dysphagia daily diary. Mean eosinophil counts fell significantly from 156 to 39 eos/hpf with budesonide. In addition, endoscopic features of edema, rings, exudates, and furrows showed significant improvement using a validated instrument. A European study used a novel budesonide effervescent tablet and viscous suspension in 76 adults with EoE. This study demonstrated an over 90% histologic response defined by <16 eos/mm^2 following 2 weeks of active drug. This study, however, failed to demonstrate significant symptom improvement compared with placebo during the 2-week treatment period.

The ease of administration and the favorable side effect profile make topical steroids an attractive first-line therapy for EoE. After withdrawal of steroids, symptoms return within 3 to 6 months (112). A randomized controlled maintenance study confirmed earlier observations regarding recurrent esophageal eosinophilia in most patients following steroid cessation. It is unclear whether the duration of remission is affected by any specific presenting feature, degree of response, or duration of initial therapy. In terms of adverse effects, esophageal candidiasis occurs in a small proportion and is usually asymptomatic. Prospective studies have demonstrated evidence of adrenal insufficiency in 0% to 15% of patients treated with long-term topical steroids. Variability in the methods used to define adrenal suppression as well as confounding by previous use of other forms of corticosteroids in these highly atopic patients are important considerations. There is concern that topical steroids can affect long-term growth in children, although greater first-pass metabolism and, therefore, safety would be expected with swallowed as compared to inhaled route of administration (113).

Although studies have demonstrated clearance of eosinophils in the esophageal mucosa with therapy, it is possible that continued immune-mediated inflammation in response to antigenic stimulation can cause ongoing inflammation and remodeling in the subepithelium. Studies with endoscopic ultrasonography have demonstrated increased thickening of the esophageal submucosa and muscularis layers in both children and adults. Prospective, adult studies in EoE have demonstrated little to no reduction in subepithelial fibrosis and transmural esophageal expansion following treatment with topical steroids for a year. Uncontrolled pediatric studies, on the other hand, have demonstrated improvement in lamina propria fibrosis in a subset of patients with topical steroids and elimination diet (22).

Systemic Corticosteroids

One of the first treatment options reported for EoE was systemic corticosteroids. Liacouras et al. (113) followed 21 pediatric patients treated with 1.5 mg/kg/day of oral methylprednisolone for 4 weeks. After 4 weeks, 65% became completely asymptomatic, and 30% had marked improvement. All patients demonstrated histologic resolution of eosinophilia. The corticosteroids were tapered over 6 weeks, and 50% of patients remained asymptomatic at 12 months' follow-up. Biopsies taken 6 months after cessation of steroid therapy demonstrated recurrence of esophageal eosinophilia to near pretreatment levels. A second pediatric study randomized 80 patients to therapy with either topical fluticasone 220 to 440 µg orally four times a day (QID) or prednisone 1 mg/kg BID (max 30 mg BID) for 4 weeks (112). The primary endpoint of improvement in a histologic score that combined severity of basal zone hyperplasia and eosinophilia was achieved in 94% of both groups. Likewise, secondary endpoints of symptom resolution (97% fluticasone and 100% prednisone) and reduction of tissue eosinophilia to <5 eos/hpf (67% fluticasone and 78% prednisone) were not significantly different in the two treatment arms. Normalization of the histologic score that factored in both eosinophilia and basal zone hyperplasia was significantly greater with prednisone (81%) than fluticasone (50%). Adverse effects were seen in 40% of the prednisone group that included Cushingoid features and weight gain, whereas 15% of the fluticasone group developed esophageal candidiasis. The lack of evidence supporting a clinical benefit of systemic steroids over topical steroids favors the use of the latter.

Montelukast

Montelukast, a leukotriene D4 receptor antagonist, has been studied in a small adult cohort with EoE. Attwood et al. (114) used montelukast in 8 adult patients with an initial dose of 10 mg daily. Seven patients showed symptom improvement with dosages between 20 and 40 mg QD with escalation to 100 mg/day in one patient after a median of 14 months. Six patients had recurrence of symptoms within 3 weeks of discontinuing or reducing therapy. Furthermore, montelukast did not change the density of eosinophils after 4 months of treatment. Common side effects included nausea, headache, and myalgias that occurred more frequently at doses higher than 40 mg/day. Recently, a randomized controlled trial evaluated the efficacy of montelukast for symptom recurrence among 41 patients who responded to induction therapy with topical fluticasone. The study endpoint was symptom remission at week 26. Although a greater proportion of patients on montelukast had sustained symptom response (40%) compared with placebo (24%), this difference was not statistically significant. Eosinophil counts were not included as a study endpoint but may not be an appropriate biomarker of effectiveness, given the mechanism of action of this agent.

Cromolyn Sodium

Cromolyn sodium (100 mg QID) was used in 14 pediatric cases of EoE. A small and nonsignificant reduction of esophageal eosinophilia was observed. Although cromolyn was well tolerated, symptoms did not improve.

Histamine-Receptor Antagonists

Kaplan et al. (115) reported complete symptom response in four of eight adults with EoE after treatment with a combined H_1 and H_2 antagonists. Previous studies have shown that antihistamines can affect eosinophil activation and release of their granules. The results of this small, retrospective series need to be confirmed because several patients were also treated with esophageal dilation and PPI therapy that may have affected symptom outcomes.

Immunomodulators

Azathioprine and 6-mercaptopurine were used in three adult EoE patients who were dependent on systemic steroids (116). One patient had predominant disease of the muscularis layer, whereas another patient had eosinophilic gastroenteritis as well as esophagitis. Eosinophilia normalized with the immunomodulators and allowed for steroid withdrawal. Recurrent eosinophilia was observed after cessation of the immunomodulator therapy.

Another novel approach is use of an antagonist of the chemoattractant receptor-homologous molecule on T_H2 cells (CRT_H2) which is a prostaglandin D_2 receptor. A selective, orally administered CRT_H2 antagonist, OC000459, was studied in a randomized controlled trial of 26 adults with EoE treated for 8 weeks (117). Eosinophil load (mean of 40 hpfs from eight biopsies) significantly but modestly decreased with active treatment from 115 to 73 eos/hpf) but not placebo. A modest but significant improvement in physician's global assessment of disease activity was noted, and the drug was well tolerated. Enthusiasm for this agent is tempered by the limited anti-inflammatory activity compared the efficacy noted with topical steroids.

Biologic Therapy

Specific mediators involved in the pathogenesis of EoE have been identified in translational studies as well as murine models. Antibodies directed against key mediators of the allergic and T_H2-mediated inflammatory response in EoE are under active investigation. Given that a significant proportion of EoE patients do not respond to steroid therapy, biologic therapies offer a novel and targeted approach. Furthermore, systemically active therapeutics have potential, conceptual advantages over topical therapy. Benefits of such agents beyond topical steroids as well as in steroid refractory subgroups are being evaluated.

IL-5 is a cytokine primarily produced by T_H2 lymphocytes that regulates the proliferation, bone marrow release, maturation, activation, and survival of eosinophils. Mepolizumab is a fully humanized monoclonal IgG antibody that selectively binds and inactivates IL-5 that demonstrated efficacy in a randomized, double-blind, placebo controlled trial in patients with hypereosinophilic syndrome. Studies have also demonstrated increased expression of IL-5 in the esophageal epithelium in EoE. An open-label trial was conducted using anti-IL5 for four adult EoE patients, three of whom had severe disease. Maximum esophageal eosinophil counts fell from 153 to 28 eos/hpf with 4 weeks of therapy (118). Less positive results were reported in a randomized controlled trial of 11 adults with EoE who were either unresponsive or dependent on corticosteroids. Mepolizumab was administered every 4 weeks with follow-up over 12 weeks. Although a statistically significant decrease was noted in both peripheral blood and esophageal eosinophilia, remission, defined by ≤5 eos/hpf, was not achieved in any patient.

Two randomized controlled trials of anti-IL-5 therapy were completed in pediatric EoE. Fifty-nine children with EoE were randomized to three doses of

mepolizumab (0.55, 2.5, and 10 mg/kg) administered intravenously every 4 weeks over 12 weeks, with one arm was chosen as a minimally effective dose to serve as a comparator (119). The primary endpoint defined by the proportion of patients with reduction in eosinophil levels to <5 eos/hpf was achieved in 8.8%. Peak eosinophil counts fell from 123 to 40 eos/hpf, with the most marked improvement interestingly seen with the 2.5 mg/kg rather than 10 mg/kg dose. In one of the largest trials in EoE, three doses of Rezlizumab were compared to placebo in 226 children with EoE (120). Active therapy led to a 59% to 67% reduction in esophageal eosinophilia compared with 24% with placebo. No difference, however, was seen in the co-primary outcome of physician global assessment with active drug when compared to placebo.

Anti-IgE therapy with omalizumab was used in an open-label trial of nine adults with eosinophilic gastroenteritis, of whom seven had both EoE and eosinophilic gastroenteritis. Significant decreases in symptoms, IgE levels (79% reduction), and peripheral eosinophilia (34% reduction) were observed. Although a nonsignificant reduction in gastric and duodenal eosinophilia was noted, there was an increase in esophageal eosinophilia. In a randomized controlled trial of 30 adults with EoE, subcutaneous omalizumab for 16 weeks did not improve either symptoms or esophageal eosinophilia (121). This study provided evidence against a significant role for IgE in the pathogenesis of EoE.

Tumor necrosis factor (TNF) expression has increased expression in EoE. Infliximab, a TNF-α monoclonal antibody, has demonstrated significant efficacy in the induction of remission and maintenance therapy of Crohn disease, another gastrointestinal T_H2-mediated chronic inflammatory condition. In an open-label trial in three patients, treatment with two doses of infliximab 5 mg/kg did not result in improvement in symptoms, esophageal eosinophilia, or tissue expression of TNF-α.

IL-13 is overexpressed in the esophageal mucosa in EoE patients and induces a substantial number of genes that overlap with the EoE transcriptome. A monoclonal antibody targeting IL-13, QAX576, was examined in a small proof-of-concept, randomized, placebo controlled trial of 23 adults with EoE given every 4 weeks for 8 weeks. The study did not meet the primary endpoint based on a 75% reduction in eosinophil density. Mean eosinophil counts, however, decreased by 60% with QAX576 compared to a 23% increase in placebo. Furthermore, the histologic improvement was maintained for 6 months following the last dose. Improvement in the EoE-related mRNA expression was identified. A second, humanized monoclonal IgG antibody selective for IL-13, RPC4046,

was examined in a randomized, double-blind, placebo controlled trial of 99 adults with EoE with weekly subcutaneous administration (180 mg, 360 mg, and placebo) for 16 weeks. RPC4046 demonstrated an overall 79% decrease in eosinophil density with both 180 and 360 mg doses, without change with placebo (122). In this study, significant improvement in endoscopic features was also evident with RPC4046 but not placebo. Significant improvement in subject's global assessment of disease activity was identified with the 360 mg dose of RPC4046.

Dietary Therapy

Diet Therapies

Diet therapy was first identified as an effective therapeutic approach in children with EoE, thereby implicating dietary antigens in the pathogenesis of EoE. Studies have subsequently identified three distinct diet approaches in both children and adults: elemental formula, allergy testing-directed, and empiric elimination diets. Diet therapy has emerged as a nonpharmacologic, first-line approach to disease management.

Elemental Diet

Diet as a therapy for EoE was initially reported in a small, proof-of-concept study of 10 children with suspected GERD with esophageal eosinophilic inflammation who failed to improve histologically and symptomatically following acid suppression or surgical fundoplication (55). At the time of this report, esophageal eosinophilia was viewed as a pathologic hallmark of GERD. In this landmark study, administration of an ELED led to substantial improvement of both symptoms and esophageal eosinophilic inflammation. The profound effect of an amino acid formula devoid of dietary protein implicated that food allergy, and not GERD, was responsible for the eosinophilic inflammation. Subsequently, uncontrolled pediatric series from several institutions have confirmed an overall 90% histologic remission in EoE. Two prospective adult studies of ELED reported a lower histologic response in approximately 75%, suggesting that nonfood allergens may be playing a role in adults with EoE (67). However, the adult trials were both limited by a 4-week treatment period, a high patient dropout caused by unpalatability of the elemental formula and nonadherence to the diet protocol.

Retrospective cohort studies as well as a meta-analysis have reported superiority of the ELED over either the empiric elimination or allergy testing-directed diet approaches discussed below (123). Limitations include the lack of

meal variety as well as poor tolerance for elemental formulations and that the majority of children required nasogastric or percutaneous gastrostomy tube feedings. While the goal of diet therapy is the elimination of specific food triggers, another major shortcoming of the ELED approach is the length of time and number of endoscopies required to identify specific triggers during food reintroduction. Symptom-based reintroduction eliminates the need for endoscopy but suffers from the limited correlation between symptom and histologic disease activity.

Allergy Testing-Directed Elimination Diet

Allergy testing-directed dietary therapy has the conceptual appeal of identification of trigger foods, thereby streamlining the empiric elimination and reintroduction process. A large, retrospective study in children utilized a combination of SPT and APT of 23 different foods to formulate an elimination diet and demonstrated a 72% histologic remission. The foods most commonly linked with EoE included milk, soy, wheat, chicken, and beef. Subsequent pediatric series have reported response rates of 53% to 65% using allergy testing-directed diets, but adult series have demonstrated substantially lower response rates. A prospective trial utilizing a combination of prick and patch testing in 22 adults with EoE achieved only a 26% remission (60). Another prospective study of 50 adults with EoE found a predictive value of 13% for SPT, suffering from both false-positive and false-negative test results (66).

Current studies do not support the widespread utilization of IgE-based allergy testing in EoE for the intent of identification of causative foods. Inconsistent response rates to testing-directed diet therapy speak to variability in patient populations, subjectivity in test interpretation, and lack of standardization of food extracts used in patch testing. Moreover, current studies have failed to identify a major role for IgE in the immune pathogenesis of EoE as evidenced by the lack of response to anti-IgE therapy in EoE (121). Novel immunologic assays to accurately identify food triggers in EoE are needed.

Empiric Elimination Diet

Given the difficulties with following an ELED and the variable response rates to skin testing to detect specific foods triggers in EoE, a number of studies have used an empiric elimination diet. The foods eliminated in this approach exclude the most common food allergens. The six (or eight) food elimination diet (SFED) eliminates cow's milk, egg, soy, wheat, peanuts/tree nuts, and fish/shellfish. First studied in children, the SFED has shown consistent effectiveness in the treatment of EoE. Kagalwalla et al. (124) first demonstrated

histologic remission in 74% of children treated with SFED. Similar histologic response rates were found in prospective adult EoE studies from the United States and Spain (125). In the Spanish study, patients were followed for up to 3 years and remained in remission while avoiding their specific trigger foods. In both adult and pediatric populations, milk, wheat, egg, and soy have been identified as the most common food triggers for EoE. Empiric elimination of single (milk), two (milk and wheat), or four food groups are being actively investigated as alternatives to the SFED.

The empiric elimination diet has demonstrated a consistently high degree of effectiveness while allowing for continued consumption of a restricted number table foods that include fruits, vegetables, meat, poultry, rice, beans, and alternative grains such as quinoa. In patients demonstrating histologic response, eliminated food groups are sequentially reintroduced while monitoring for disease recurrence using endoscopic biopsies. The current requirement for repeated endoscopies during the reintroduction is a considerable drawback to this approach. Practically, the elimination diet can be onerous because of concerns with dietary contamination, psychosocial impact of restricted diets, and costs of allergen-free food products. Incorporation of a dietician or allergist in patient education and dietary monitoring likely improves the success of the elimination diet approach. A number of office-based methods to detect disease activity without endoscopy are being developed (126).

Practical Implementation of Diet Therapy in the Management of Eosinophilic Esophagitis

Because there are no controlled studies comparing dietary with steroid therapy in EoE, the choice of treatment approach is currently individualized, based on a discussion with the patient. The dietary approach does require a highly motivated patient and physician. Studies across medical disciplines have demonstrated the widespread patient acceptance for the use of diet interventions to manage medical conditions. Many patients find the concept of remedying their disease by eliminating a dietary trigger more appealing than taking a drug to counteract the downstream inflammatory response. Furthermore, when discussing the dietary approach, it is important to emphasize that the strict elimination of multiple foods is for a finite period. The "big picture," long-term goal is the identification and long-term elimination of one or two food groups. Once a food trigger has been identified, occasional dietary "indiscretion" is likely acceptable, in distinction to patients with food-associated anaphylaxis. Small case series have described tolerance to baked milk in patients with cow's milk–mediated EoE

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(127). Moreover, because progress is made in the understanding of the pathogenesis of EoE, newer therapeutic options will eventually supplant the current management approaches.

Endoscopic Therapy

Esophageal Dilation

Esophageal dilation is a therapeutic modality which has primarily been used in adult EoE patients with strictures. Several patients have required hospitalization for chest pain or esophageal perforation following esophageal dilation (Fig. 40.3) (128). In the reported cases, the perforations have been managed conservatively without need for surgical repair. Whereas swallowed corticosteroids and diet modification therapy presumably target the inflammation associated with the pathogenesis of EoE, esophageal dilation targets the fibrostenotic complications of the disease. Several case series suggest that esophageal dilation is well tolerated by patients and provides long-lasting symptomatic relief despite having no effect on mucosal eosinophilia (129). Esophageal dilation offers an important adjunct to topical corticosteroids and/or dietary therapy and may be considered in patients unresponsive to initial medical or diet therapy. Furthermore, a small randomized controlled trial demonstrated that esophageal dilation combined with medical therapy did not improve symptom response compared to medical therapy alone. Although effective at relieving dysphagia, esophageal dilation carries risks of postprocedural chest pain and uncommon but significant complications that should be discussed with patients.
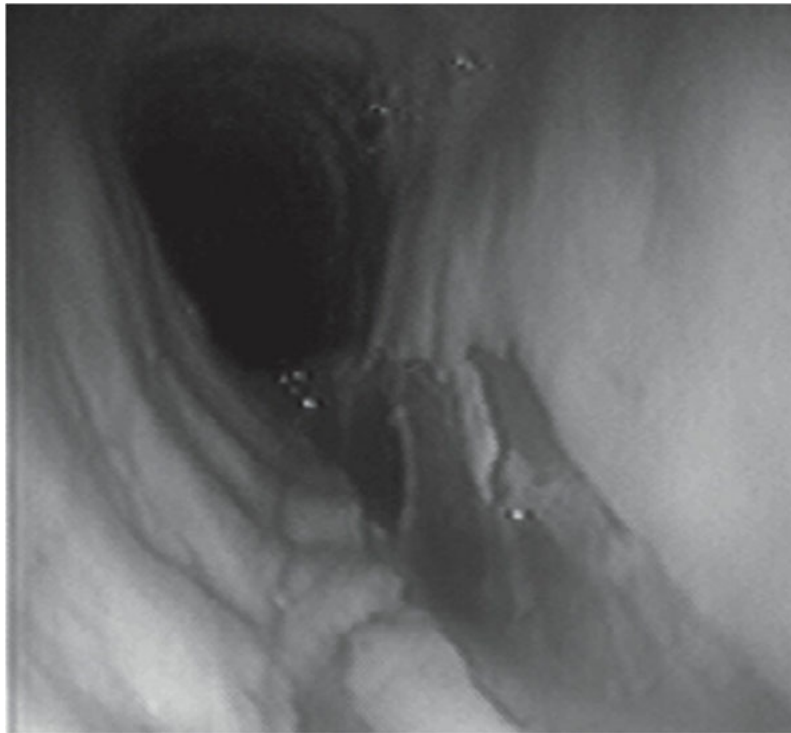
■ **FIGURE 40.3** Endoscopic photograph showing mucosal tear.

Suggested alogorithm for treatment of eosinophilic esophagitis

Suspected EoE

PPI BID × 6–8 wk

Symptom relief & normal histology

EGD with Bx

≥15 eosinophils/high-power field

PPI responsive EoE versus GERD

EoE

Topical steroid Dietary therapy

Persistent symptoms and/or pathology
R/O Candida/noncompliance

Follow-up

Elimination or elemental diet
Systemic steroid
Esophageal dilation
High-dose topical steroid
Biologic therapy

Symptomatic & histologic remission

Consider maintenance therapy

■ **FIGURE 40.4** Algorithm for the treatment and evaluation of eosinophilic esophagitis (EoE). BID, twice a day; Bx, biopsy; EGD,

esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

◼ CONCLUSION

EoE is an emerging clinical problem, and treatment is effective at reducing symptoms as well as tissue eosinophilia. Although the risk of not treating an asymptomatic or minimally symptomatic patient is currently unknown, sequella, including fibrosis, narrow caliber esophagus, and stricture formation, are well described. Furthermore, symptoms that impair quality of life as well as complications of malnutrition, food impaction, and esophageal perforation have been reported. The degree to which the structural alterations are reversible with medical or dietary therapy is uncertain. Spontaneous remission appears to occur infrequently.

A clinical approach to EoE begins with an increased awareness of the disease and its manifestations. Figure 40.4 illustrates a proposed algorithm for EoE management. The diagnosis should be considered in a child presenting with vomiting, food refusal, and abdominal pain, especially if the symptoms have not improved with empiric therapeutic trials of acid suppression. The diagnosis should be strongly entertained in both children and adults with dysphagia and food impactions, regardless of the presence or absence of heartburn. Other presentations include atypical chest pain and heartburn that do not respond to empiric PPI therapy.

Once the presence of increased esophageal eosinophilia (generally greater than 15 eos/hpf) has been demonstrated, patients should undergo an 8-week trial of acid-suppression therapy to see if this results in clinical and histologic improvement. This recommendation is based on observations that some patients with esophageal eosinophilia respond both symptomatically and histologically to PPI therapy, an entity called PPI-REE. If symptoms and eosinophilia persist despite adequate acid suppression, the various treatment options for EoE are discussed with patients. The most common treatment approaches are medical therapy with swallowed topical corticosteroids or dietary therapy with empiric elimination diet or is severe cases, ELED. Allergy consultation has been useful to help treat patients with other allergic diathesis and, in some cases, monitor for allergic symptoms during food reintroduction. The role of treatment of aeroallergens (e.g., allergen avoidance, nasal steroids, immunotherapy) in EoE patients remains speculative at this time. Esophageal dilation is performed cautiously for strictures that do not respond to medical or dietary treatment.

Patients may benefit from maintenance therapy given the high rates of symptomatic recurrence of EoE in both children and adults.

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Chronic Cough

RACHEL E. STORY AND JENNIFER S. KIM

INTRODUCTION

Cough is the most common complaint for which Americans see a primary care physician (1). In the United States, the cost of over-the-counter medications to treat cough is estimated to exceed $2 billion on an annual basis (2). The differential diagnosis, diagnostic evaluation, and treatment of cough differ in children and adults. This chapter focuses on chronic cough and discusses in children and adults separately.

Cough is a reflex response of the lower respiratory tract that is mediated by cough receptors of the airways. Cough serves to clear secretions and particles from the airway and protect against aspiration. Cough receptors are found in the airways, including the trachea, bronchi, distal small airways as well as the pharynx, larynx, paranasal sinuses, diaphragm, pleura, pericardium, and stomach. Chemical receptors are stimulated by acid, heat, and capsaicin-like compounds. Mechanical receptors are triggered by touch and displacement. When a chemical or mechanical cough receptor is stimulated, an impulse travels to the "cough center" in the medulla via the vagus nerve to trigger cough via vagal, phrenic, and spinal motor nerves (3).

COUGH IN ADULTS

Cough in adults (patients ≥ 15 years of age) is categorized in three groups: acute cough lasting <3 weeks, subacute cough lasting 3 to 8 weeks, and chronic cough lasting >8 weeks. Detailed discussion of each group is beyond the scope of this chapter. Also not in the scope of this chapter is cough in smokers, often caused by chronic obstructive pulmonary disease (COPD), defined as persistent airflow limitation because of irritant-induced chronic inflammation (4). Acute cough is usually infectious in nature. Subacute cough is often postinfectious but can also represent the onset or exacerbation of conditions known to cause chronic cough. This chapter focuses on chronic cough in nonsmokers because it is one of the most common reasons patients seek care from a respiratory specialist.

Chronic cough occurs in 10% to 20% of adults and can be debilitating (5). Complications of cough include almost every organ system and have been shown to significantly decrease quality of life (6–8). In adults, three conditions cause the majority of cough in nonsmoking adults who are not on an angiotensin-converting enzyme inhibitor (ACE-I): upper airway cough syndrome (UACS), asthma, and gastroesophageal reflux (GER). In patients with a normal chest radiograph and no symptoms suggesting a specific etiology of cough, most groups recommend investigation and treatment of UACS, asthma, and GER prior to the investigation of less common causes of cough. A comprehensive differential diagnosis for chronic cough in adults is included in Table 41.1.

Upper Airway Cough Syndrome

UACS was formerly known as the postnasal drip syndrome. UACS alone or in combination with other conditions is the most common cause of chronic cough (9). Postnasal drip, the drainage of secretions from the nose or paranasal sinuses into the pharynx, may causes cough via mechanical stimulation of the cough reflex, increased cough receptor sensitivity, or coexistent inflammation in the lower airways (10,11). The causes of UACS include allergic rhinitis, nonallergic rhinitis, vasomotor rhinitis, nonallergic rhinitis with eosinophilia, rhinitis medicamentosa, gustatory rhinitis, infectious rhinitis, infectious sinusitis, allergic fungal sinusitis, rhinitis of pregnancy, and chemical/occupational rhinitis. These conditions, their diagnosis and specific treatments, are discussed in detail in Chapters 26 and 27.

History and physical examination alone frequently will not accurately identify the cause of chronic cough. Often, patients with UACS will report the sensation of mucus dripping down their throat and frequent throat clearing. On physical examination, mucoid or mucopurulent secretions may be present, and cobblestone changes in the oropharynx maybe noted. However, 20% of patients with cough due to UACS do not report symptoms of postnasal drip, and more than 50% do not have physical examination with characteristic changes (12). A prospective study of chronic cough in adults found that medical history regarding the character and timing of cough is of little value in determining the etiology of cough (13).

TABLE 41.1 DIFFERENTIAL DIAGNOSIS OF COUGH IN ADULTS

Upper airway cough syndrome (UACS)
- Allergic rhinitis

- Nonallergic rhinitis
- Vasomotor rhinitis
- Nonallergic rhinitis with eosinophilia (NARES)
- Rhinitis medicamentosa
- Gustatory rhinitis
- Infectious rhinitis
- Infectious sinusitis
- Allergic fungal sinusitis
- Rhinitis of pregnancy
- Chemical/occupational rhinitis

Asthma

GER

Nonasthmatic eosinophilic bronchitis

Tracheobronchial collapse

Irritant inhalation/occupational and environmental considerations
- Tobacco smoke (personal use or environmental exposure)
- Biomass combustion particles
- Occupational exposures (hard metal disease, asbestosis, beryllium, bioaerosols endotoxin or fungal glycans)

Medications
- ACE inhibitors
- β-Blockers

Pulmonary infections
- Pneumonia
- Tuberculosis
- Recurrent viral bronchitis

COPD/chronic bronchitis

Bronchiectasis

Aspiration

Interstitial lung disease

Cystic fibrosis

Ciliary disorder

Immunodeficiency

Sarcoidosis

Vasculitis

Respiratory tumors

Psychogenic cough

Tic (Tourette)

Vocal cord dysfunction

Increased cough receptor sensitivity

Otogenic causes (Arnold's ear)

Occult heart failure

Idiopathic

Treatment of UACS depends on its etiology. If there is an apparent etiology for UACS such as chronic sinusitis or allergic rhinitis, appropriate treatment with antibiotics or intranasal steroids should be instituted. However, if a specific etiology is not clear, a diagnostic/therapeutic trial with antihistamine/decongestants or nasal steroids is recommended by the American College of Chest Physicians (ACCP) prior to investigating less common causes of cough (9). Cough due to UACS typically resolves over a period to days to weeks with treatment. If a patient's cough does not respond to empiric treatment and UACS is still suspected, the ACCP recommends a sinus computed tomography (CT) because chronic sinusitis may cause a cough without typical sinusitis symptoms.

Asthma

Asthma should be considered in all adults with chronic cough. Although cough is a common symptom of asthma, most patients experience dyspnea and wheezing in addition to cough. Still, some patients with asthma have cough as their predominant symptom, and this condition is referred to as cough-variant asthma (CVA). Patients with CVA have a more sensitive cough reflex than healthy volunteers and patients with typical asthma (14). If reversible airflow obstruction is found on spirometry, treatment with inhaled corticosteroids and bronchodilators should be instituted. At times, leukotriene antagonists, long-acting β agonists, and oral steroids may be used, as discussed in Chapters 34 to 36.

In a patient with a normal physical examination and normal spirometry, a methacholine inhalation challenge (MIC) essentially rules out the diagnosis of asthma because it has a negative predictive value close to 100% (15). There is a risk of a false-positive study; one prospective study of chronic cough in adults found that the MIC was falsely positive 22% of the time (16). Fractional exhaled nitric oxide (FeNO) is a noninvasive marker of allergic airway inflammation. Studies on the usefulness of FeNO in chronic cough are conflicting with some studies finding that increased FeNO levels predicted responsiveness to inhaled corticosteroids, whereas others find no such relationship (17–21). Additionally, low FeNO levels do not exclude a diagnosis of asthma (17). Thus, diagnosis of CVA is made only after resolution of cough with specific asthma treatment (22). A diagnostic/therapeutic trial of asthma therapy is often performed. If MIC testing is not performed, nonasthmatic eosinophilic bronchitis cannot be ruled

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out as the etiology of the cough. This is discussed in detail later in this chapter.

Gastroesophageal Reflux

GER causes cough via chemical and mechanical irritation of the upper respiratory tract, irritation of the lower respiratory tract via microaspiration, and by stimulating an esophageal-bronchial cough reflex (23). The proportion of chronic cough attributable to GERD varies widely with estimates ranging from 2% to 81%, but is generally thought to be the most common cause of chronic cough after UACS and asthma (24,25). History regarding the character and timing of cough is not sufficient to distinguish a cough from GER from other causes of cough. One study found that cough due to GER occurs at night in only a minority of patients (13). In addition, GER is "silent" with no gastrointestinal symptoms in up to 75% of patients, suggesting that nonacid reflux may play a significant role in symptoms (26).

Empiric treatment with medical antireflux therapy is warranted when GER is the likely cause of cough. This includes patients with typical symptoms of regurgitation and heartburn and those with a high likelihood of GER-related cough, that is, patients in whom asthma, nonasthmatic eosinophilic bronchitis, and upper UACS have been ruled out following an algorithmic approach. In 2016, the ACCP updated guidelines for management of reflux-cough syndrome and recommend the following: dietary modification to promote weight loss in overweight and obese patients, elevation of the head of the bed and avoiding meals within 3 hours of bedtime, and the use of proton pump inhibitors, H_2-receptor antagonists, or antacid therapy only in patients who report heartburn and regurgitation (25). Proton pump inhibitors alone were not recommended for treatment of cough suspected owing to reflux because they are unlikely to resolve the cough (25,27). A 3-month trial of medical antireflux therapy is recommended for patients with chronic cough suspected to be caused by reflux. Esophageal manometry and pH-metry is recommended only in those with high clinical suspicion of reflux who fail medical reflux therapy and in patients being considered for surgical management (antireflux or bariatric surgery depending on the patient) (25). Surgery is recommended in patients with chronic cough who fail medical therapy and have abnormal esophageal acid exposure determined by pH-metry (25). When UACS, asthma, and GER have been ruled out as a cause of cough, other diagnosis should be investigated depending on the clinical picture.

Nonasthmatic Eosinophilic Bronchitis

Nonasthmatic eosinophilic bronchitis is a common cause of chronic cough characterized by corticosteroid responsive eosinophilic airway inflammation without variable airway obstruction or airway hyper-responsiveness. Studies found that between 10% and 30% of cases of chronic cough are caused by nonasthmatic eosinophilic bronchitis (28–30). Patients with nonasthmatic eosinophilic bronchitis have chronic cough with no reversible airway obstruction on spirometry, normal airway hyper-responsiveness on MIC, and sputum eosinophilia. This condition was likely unrecognized in the past and misdiagnosed as asthma if MIC was not performed because cough typically resolves with inhaled corticosteroids.

Primary Pulmonary Disease

Primary pulmonary disease is a less common cause of chronic cough with varying frequency, depending on the population studied. One prospective study of chronic cough found bronchiectasis and interstitial lung disease (ILD) as the etiology of cough in 16% of participants (31). In this study, a productive cough and an abnormal chest radiograph were predictive of a primary pulmonary cause of cough; however, other groups have not found chest radiograph to be predictive.

Bronchiectasis

Acute and chronic infection resulting in the permanent dilation of bronchi cause most cases of bronchiectasis (32). Owing to improvements in the prevention and treatment of childhood infections with immunizations and antibiotics, there is a decrease in the incidence of bronchiectasis in immunocompetent individuals (33). In developed countries, patients with bronchiectasis often have an underlying disorder that predisposes them to the development of bronchiectasis, including cystic fibrosis (CF), allergic bronchopulmonary mycosis, hypogammaglobulinemia, HIV, primary ciliary dyskinesia, chronic mycobacterium avium complex (MAC) infection, aspiration, rheumatoid arthritis, inflammatory bowel disease, and α-1 antitrypsin deficiency (32). Patients typically present with a chronic productive cough, and diagnosis is made when characteristic changes are found on high-resolution CT of the chest (34). Treatment includes the use of bronchodilators, chest physiotherapy, antibiotics, and mucolytics.

Interstitial Lung Disease

ILDs are a heterogeneous group of pulmonary disorders that involve the alveolar

and perialveolar tissues. They can be classified into those with known causes and those without a known cause. Known causes of ILDs include environmental and occupational exposures, such as asbestosis, hypersensitivity pneumonitis, and beryllium. Unknown causes of ILDs include idiopathic pulmonary fibrosis, sarcoidosis, and ILD associated with collagen vascular disease. In patients with chronic cough, ILD should be investigated after more common causes of cough have been ruled out, especially if history or a chest radiography is suggestive (35).

Lung Tumors

While cough is often a presenting symptom of lung cancer, it is still a rare cause of cough (≤2%) in patients presenting with chronic cough (36). In those with known risk factors for lung cancer, including cigarette smokers, those with passive cigarette smoke exposure, exposure to asbestos and radon, COPD, and a family history of lung cancer, a chest radiograph should be obtained. Likewise, individuals with known cancer that may metastasize to the lung should have chest radiography performed. CT scans and bronchoscopy may be required if there is a high degree of suspicion and a normal chest radiograph.

Infection

Infection is not a major cause of chronic cough, but it must be considered in the differential in the appropriate clinical context. Because cough is the most common symptom in active tuberculosis (TB), it should be considered in any patient with cough lasting 2 to 3 weeks if the likelihood of active TB is high (37). High-risk groups include those living in endemic areas, HIV seropositive individuals, prisoners, and those living in nursing homes. It is important to recognize that elderly patients will present with productive cough but are less likely to have fever, sweating, hemoptysis, and a positive tuberculin skin test result (38). Thus, one must have a high index of suspicion when considering TB in an elderly population. If TB is suspected a tuberculin skin test or interferon γ-releasing assay, chest radiograph, and sputum smears and cultures for acid-fast bacilli should be obtained. Pertussis is commonly thought of as a disease of children, but can cause chronic cough in adults. In a study of adults presenting to the emergency department (ED) complaining of cough for >2 weeks, 21% were found to meet serologic criteria for pertussis infection (39). Endemic fungi and parasitic disease should also be considered in patients visiting or residing in endemic locations.

Aspiration

Oral-pharyngeal dysphagia resulting in aspiration can cause chronic cough. Many patients with aspiration cough when eating and drinking, but aspiration can also be "silent" with no associated cough with feeding. Aspiration is common after acute stroke with up to 38% showing aspiration on video fluoroscopic swallow evaluation (40). Other conditions in which aspiration should be suspected include neurologic impairment such as Parkinson disease, anoxia, and head trauma, and postoperative aspiration after cervical spine surgery and head and neck cancer surgery (41). Elderly individuals who are bed bound and require assistance for oral care are also more likely to have aspiration and at increased risk for cough due to aspiration (42,43). If aspiration is suspected, referral to a speech-language pathologist is recommended for an oral-pharyngeal swallow evaluation.

Angiotensin-Converting Enzyme Inhibitor Cough

Cough is a clearly established side effect of ACE-I medications (44). It has been reported to be develop in 5% to 35% of individuals taking an ACE-I and is more likely in women and nonsmokers (45). Symptoms can start within hours of taking the medication or may not appear until months later. Treatment is to discontinue the medication, and cough typically resolves within days but has been reported to continue up to 4 weeks (44). Angiotensin II receptor antagonists are not associated with an increased risk of cough, even in patients who had cough on ACE-Is (45,46).

Psychogenic (Habit) Cough

There is no standard definition for psychogenic cough in the medical literature. While some authors equate psychogenic cough with habit cough, others consider them separate disorders. ACCP clinical practice guidelines recommend that a diagnosis of habit or psychogenic cough only be made after an extensive evaluation rules out other disorders, including tic disorders, and when the cough improves with psychiatric therapy or behavior modification (47). If cough does not respond to psychiatric therapy or behavior modification, a diagnosis of unexplained cough should be made rather than habit or psychogenic cough.

Unexplained Chronic Cough

Unexplained chronic cough is defined as cough that persists longer than 8 weeks and is unexplained after investigation, supervised therapeutic trials conducted

according to published best practice guidelines. The 2016 ACCP guidelines recommend treatment with multimodal speech pathology therapy (48). In addition, studies suggest unexplained chronic cough maybe due to "cough hypersensitivity syndrome," a disorder of sensory neural function that has been shown to respond to gabapentin (49). The ACCP recommends a therapeutic trial of gabapentin after risks and benefits have been discussed with the patient (48).

APPROACH TO THE DIAGNOSIS AND MANAGEMENT OF CHRONIC COUGH IN ADULTS

Several groups have studied prospective diagnostic and treatment pathways with successful treatment of chronic cough in up to 98% of patients (12,16,31,50–52). Published results from specialist cough clinics, most using a treatment algorithm, found 9 of 12 groups had a success rate >90% in the treatment of chronic cough (53). Less success was reported in patients referred to a general respiratory clinic when a treatment protocol was not used with 43% of patients reporting persistent symptoms at follow-up (54). Treatment pathways usually focus on the three leading causes of chronic cough in nonsmoking adults who are not on an ACE-I: UACS, asthma, and GER. A significant number of patients may have multiple causes for their cough. Chronic cough was because of two or more conditions in 8% to 29% of patients in prospective studies (12,16,31,50–52).

The ACCP recommends the following approach to the management of chronic cough (Fig. 41.1) (55). All patients with complaint of chronic cough should have a history, physical examination, and chest radiograph performed. If patients are smokers or taking an ACE-I, the offending agent should be discontinued, and if cough persists, further evaluation should occur. If a cause of cough is suggested by history, physical examination, or chest radiograph, it should be investigated and treated. If there is an inadequate response to initial treatment, investigation of UACS, asthma, nonasthmatic eosinophilic bronchitis, and GER should occur.

For UACS, empiric treatment with antihistamine/decongestant is recommended. Asthma should be evaluated with spirometry, bronchodilator reversibility, and MIC if needed, or treated empirically with inhaled corticosteroids, bronchodilators, and/or leukotriene receptor antagonist. Nonasthmatic eosinophilic bronchitis should be investigated with sputum eosinophils in the setting of a normal MIC or treated empirically with inhaled corticosteroids. GER should be treated empirically with diet and lifestyle modification and the use of proton pump inhibitors, H_2-receptor antagonists, or

antacid therapy in patients who report heartburn and regurgitation. If there is an inadequate response to the preceding treatment, further investigation should occur, and one should consider rare causes of cough. Because cough is often multifactorial, all partially effective treatments should be maintained.

PEDIATRIC COUGH

As in adults, cough is one of the most common symptoms for which parents consult their child's primary care physician. However, based on the available published medical literature, the causes and management of cough in children differ considerably to that in adults. Overall, pediatric cough has been researched relatively poorly despite its high prevalence.

Characterization of Cough

Cough in children can be characterized by three defining aspects: duration, quality, and potential for underlying disease (11,56).

Duration

Chronic cough in children aged <15 years according to the ACCP evidence-based clinical practice guidelines is defined by a daily cough occurring for >4 weeks (57). The rationale for this is that cough due to acute respiratory infections (ARI) resolve within 1 to 3 weeks in most children (58,59). Only approximately 5% of cough following an ARI lasts more than 4 weeks (58,60). This chapter focuses primarily on chronic cough.
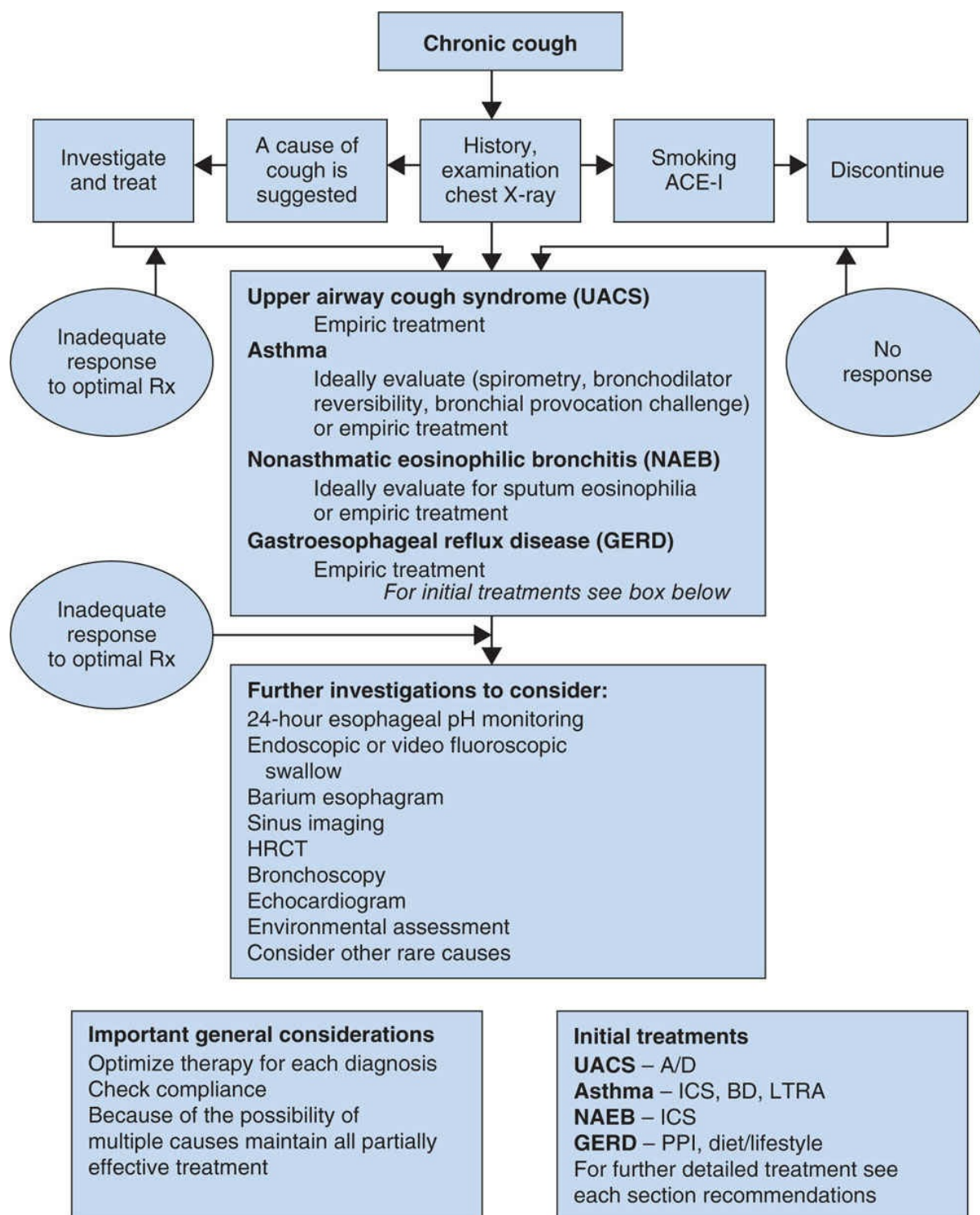
FIGURE 41.1 Management of chronic cough in adults. ACE-I, angiotensin-converting enzyme inhibitor; A/D, antihistamine/decongestant; BD, bronchodilator; ICS, inhaled corticosteroid; HRCT, high-resolution chest CT scan; LTRA, leukotriene receptor antagonist; PPI, proton pump inhibitor. (Reproduced with permission of the American College of Chest Physicians, from Pratter MR, Brightling CE, Boulet LP, et al. An empiric integrative approach to the management of cough. *Chest.* 2006;129[1]:222S–231S; permission conveyed

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Quality

Characteristics such as barking or croupy, staccato, or paroxysmal cough are classically taught, respectively, as indicators of croup, infantile chlamydia, and pertussis. However, there are limited data on the reliability of these descriptors except for the distinction between dry and wet/moist cough, which has been validated (61). Brassy cough has been shown to be highly specific for tracheomalacia (61). In contrast, parental reports of nocturnal cough have been found to be discordant from objective measures, such as recordings (62).

Potential for Underlying Disease

Cough may be expected, specific, or nonspecific.

In *expected* cough, the presence of cough is expected (or normal), such as after an ARI. Children aged <5 years have 3.8 to 5 ARIs per year, whereas adults have only 2 (63).

In *specific* cough, the etiology is usually evident from coexisting symptoms or signs. Examples would include cardiac murmur (indicating cardiac disease), digital clubbing (suppurative lung disease), failure to thrive (immunodeficiency or CF), and feeding difficulties or neurodevelopmental abnormalities (aspiration). Chronic productive purulent cough is always pathologic and must be investigated for possible bronchiectasis and evaluate for treatable causes, such as CF and immune deficiency (57).

In contrast, *nonspecific* or isolated cough has been defined as usually dry cough without a serious underlying condition.

The challenge for the physician is to determine when cough is abnormal. Healthy children cough from 1 to 34 times per day (60). Cough is subject to the period effect (spontaneous resolution), and the therapeutic benefit of placebo treatment for cough has been reported to be as high as 85% (64,65). Children have also been found to be more likely to cough under certain psychologic settings (66).

A detailed clinical history is paramount in the evaluation. Historical aspects should include frequency, severity, time course, diurnal variability, age of onset, relationship to meals, and presence of sputum, wheezing, and/or associated acute respiratory symptoms. History of passive smoke exposure should be elicited because 50% of children >2 years in families with two smokers will have significant cough (67).

Health care providers must also take into account parental perception and expectations because the reporting of cough is likely to be biased (68). Perceived severity of cough may relate closely to its effect on parents or teachers and, therefore, plays an important role in the parental pursuit of medical consultation.

Etiology

The three most common causes of chronic cough in adults (UACS, asthma, and GER) are less common in children.

The use of *isolated* chronic cough in children may indicate CVA, the diagnosis of which should be one of exclusion, particularly in the absence of other immunoglobulin E-mediated disease. The following diagnostic criteria have been proposed to identify which children with chronic isolated cough are more likely to have asthma (69):

1. Abnormally increased cough without evidence of other nonasthma diagnosis

2. Clear response to a therapeutic trial of asthma medications

3. Relapse of symptoms upon stopping medications with a subsequent second response after resuming them

4. Presence of atopic eczema, positive aeroallergen prick tests, and/or parental (especially maternal) history of asthma.

GER is infrequently the sole cause of pediatric cough, based on the little data available in the medical literature. However, cough and GER can precipitate each other, and it is difficult to differentiate cause and effect (70).

Sinusitis is not associated with cough once atopy and physician-diagnosed allergic rhinitis are controlled for (71).

Protracted bacterial bronchitis (PBB), found in 40%, was the most common final diagnosis among one prospective cohort (72). The proposed clinical definition of PBB is as follows: the presence of isolated chronic moist cough, resolution of cough with appropriate antibiotics, and absence of pointers suggestive of alternative specific cough.

The other primary diagnoses among the aforementioned cohort (found in more than one patient) include bronchiectasis, aspiration disorders, and *Mycoplasma pneumoniae* infection (56,72). Other potential causes in children include a postviral syndrome, exposure to environmental tobacco smoke or other pollutants, foreign body inhalation, airway malacia, medications (i.e., ACE-Is), psychogenic disorders, and the Arnold ear-cough reflex (57). A chronic cough

that first began after an episode of choking, or that began suddenly while eating or playing (especially in a preschool-aged child), suggests the possibility of foreign body aspiration.

Specific Cough

Specific cough should be further evaluated depending on the associated symptoms or signs present. These may include (and are not limited to) sweat chloride test, immune function studies, barium swallow, video fluoroscopy, pH probe, bronchoscopy ± lavage, echocardiography, complex sleep polysomnography, and high-resolution chest CT scan (HRCT). The risks and benefits of chest HRCT in children must be weighed because children have 10 times the increased risk of lifetime cancer mortality secondary to medical radiation compared to middle-aged adults (73). Moreover, if sedation is required, that incurs additional potential risk. However, the yield for diagnosing bronchiectasis by chest HRCT in children with chronic moist cough is very high (12). It is important to note that next to asthma, CF is the second most common chronic inflammatory airway disease, particularly among Caucasians. The severity and progression of airway disease can be highly variable. Classic, mild, and atypical CF has features that overlap with allergic/immunologic diseases. Moreover, not all patients with CF have diagnostic sweat tests. Genetic analysis should be pursued with equivocal levels of sweat chloride.

Nonspecific Cough

If the child's chronic cough is nonspecific, there are two approaches to further management. One would be "watch, wait, and review," particularly because the placebo effect on cough has been reported to be quite high (57,65). One randomized controlled trial reported that "parents who wanted medicine at the initial visit reported more improvement at follow-up, regardless of whether the child received drug, placebo, or no treatment" (74). Another prospective cohort study revealed that 24% of children had spontaneous resolution of cough. Frequent reevaluation should be performed because specific etiologic pointers may emerge (72). Cough pointers can be used to differentiate specific from nonspecific cough, recognition of which depends on physician expertise and caregiver history (75). Examples include cardiac abnormalities, digital clubbing, failure to thrive, neurodevelopmental abnormalities, fever, immunodeficiency, feeding difficulties, or history of TB exposure. Additional lung-specific symptoms characterized as cough pointers include chest pain, daily moist or productive cough, hemoptysis, abnormal cough characteristics (brassy,

paroxysmal, posttussive emesis, staccato, and cough from birth), recurrent pneumonias, hypoxia/cyanosis, exertional dyspnea, or dyspnea/tachypnea at rest. Physical findings like a chest wall deformity and abnormal auscultatory findings or abnormal test results (chest radiograph and pulmonary function test) would also warrant further investigation.

The second approach would be a trial of medical therapy, depending on the quality of the cough. Systemic reviews based on a few randomized controlled trials found high-quality evidence that in children aged ≤14 years, the management or testing algorithm for chronic cough should differ depending on the associated characteristics of the cough and clinical history (76). However, there is no evidence as to whether such algorithms should depend on duration (beyond 4-week definition) or severity of cough.

Use of Algorithms in Evaluation of Cough

In a 2013 multicenter controlled trial in Australia, 272 children (mean ± standard deviation age: 4.5 ± 3.7 years) were randomized to 1 of 2 arms: early versus delayed implementation of the cough algorithm as applied by respiratory specialists (77). Children in the early-arm group were managed in a mean of 1.94 ± 1 weeks and those in the delayed-arm group in 5.1 ± 1.8 weeks. The proportion of children who were cough free at week 6 (primary outcome) was significantly (P < 0.0001) higher in the early-arm group (54.3%) compared with the delayed-arm group (29.5%). Of the children with nonspecific cough (i.e., cough without any specific cough pointers), the three most common primary diagnoses were natural resolution (14.6%), habit cough (4.9%), and pertussis (3.5%). The three most common primary diagnoses in those with specific cough (i.e., specific cough pointers present) were PBB (41.6%), asthma or reactive airway disease (16.4%), and bronchiectasis (5.7%). Using the protocol, the algorithm identified 85% with simple etiology without any specialist investigations.

Wet Cough

The ACCP clinical practice guidelines suggest a 10-day trial of antibiotics for a wet cough (57). PBB was the most common final diagnosis among a cohort of young children with chronic cough (72). A 2016 systemic review indicated that treatment with a 2-week course of antibiotics directed against common bacterial pathogens (*Haemophilus influenzae, Moraxella catarrhalis,* and *Streptococcus pneumonia*) was sufficient for treatment of chronic wet cough (76). The most common antibiotic used was amoxicillin-clavulanate, but the choice of antibiotic should reflect local bacteria types and sensitivities. There is low-quality evidence

that a longer course, up to 4 weeks, may be required in a minority of children. One could advocate shorter initial courses in our current era of antimicrobial stewardship. Further evaluation and referral to a major medical center should be undertaken when chronic cough does not resolve after 4 weeks of appropriate antibiotic treatment or if specific cough pointers develop. Of note, it is also important to consider the geographical setting, specifically with regard to prevalence of TB.

Dry Cough

If a dry cough is present, particularly in a child at risk for asthma, a trial of inhaled corticosteroids is recommended (400 µg/day budesonide, 200 µg/day fluticasone, or equivalent) (57). Cough related to asthma is expected to resolve within 2 to 7 days. Therefore, a trial lasting 2 to 4 weeks would be reasonable. If unresponsive, increased doses are not indicated. Rather, the medication should be stopped and other diagnoses considered. On the other hand, given the favorable natural history of cough, a so-called positive response should not be assumed to be because of the medication tried. Once resolution of the cough has been demonstrated, it would be reasonable to trial the patient off medications.

Cough may also be voluntarily induced by older children because it has been found in adults to be cortically modulated, but this unlikely to be a factor in younger children (<4 years) (78). The absence of cough when asleep or when the child is distracted would be suspicious for habit cough. The classic presentation of habit cough syndrome is that of a harsh, barking, repetitive cough that occurs several times per minute for hours on end, which resolves once the patient is asleep (79).

Symptomatic Treatment

The American Academy of Pediatrics advises against the use of codeine and dextromethorphan for symptomatic treatment of any type of cough for children (80). Over-the-counter cough remedies have been associated with significant morbidity and mortality (81).

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Sleep Disorders in the Allergic Patient

RAHUL SHARMA AND LISA WOLFE

In the fourth century, biblical scholars believed that sleep was "the incomplete experience of death." The modern understanding that sleep is an active, complex, and essential behavior did not begin until the use of electroencephalography (EEG), which highlighted differences between wake and sleep (1).

SLEEP ARCHITECTURE

In mammals and birds, sleep is broadly divided into rapid eye movement (REM) and nonrapid eye movement (NREM) sleep. These stages are easily discerned with the help of EEG and electromyography (EMG) (2). The classic architecture of a full night's sleep was first reported in 1957 (3). The side-to-side REMs during sleep were discovered in 1953, and further study associated this REM sleep with dreaming, heart rate variability, irregular breathing, and muscle paralysis. Research elucidated that REM sleep occurred three to four times per night and occupied 20% to 25% of sleep time in healthy adults. In 1968, a formal protocol was developed for scoring sleep stages, combining EEG, EMG, and electrooculography (4).

Typical sleep architecture in a healthy adult is demonstrated in Fig. 42.1. Sleep onset is associated with NREM sleep that is composed of three stages: N1, N2, and N3. N3 is also referred to as slow-wave sleep (SWS). During sleep onset, N1 sleep is seen with its characteristic slow rolling eye movements and easy arousability. N2 sleep is seen soon after and is defined by a specific EEG pattern referred to as K-complexes and spindles. It becomes more difficult to awaken the sleeper. N3 follows with the characteristic EEG slow waves and is associated with physiologic events, including endocrine changes such as growth hormone release. NREM sleep becomes a bridge to initiate stage REM (5).

A complete cycle of NREM to REM sleep lasts approximately 90 minutes,

and there are three to four cycles per night. SWS predominates at the beginning of the night and is virtually gone by the final cycle. Stage REM is minimal during the first cycle and increases to the highest concentration in the early morning. Maturity also affects the architecture of sleep. With aging, there are significant reductions in SWS and sleep continuity. SWS decreases from 24% to 30% to 16% of total sleep time (TST), and wake after sleep onset time increases from 2% to 4% to 17%. The percentage of REM sleep remains stable at 20% to 25% of TST (6).
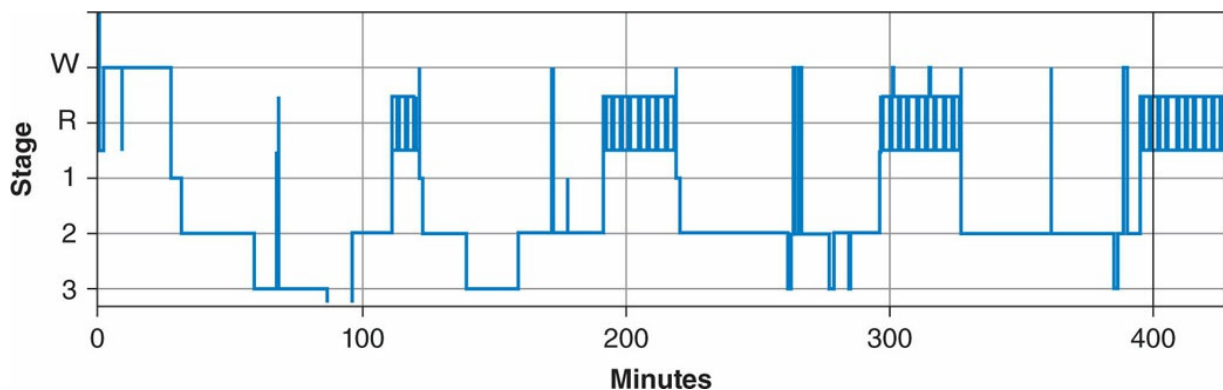
■ **FIGURE 42.1** A representative sample of sleep from a healthy young adult without sleep complaints. *W,* wake; *1,* N1 (NREM) sleep; *2,* N2 (NREM) sleep; *3,* N3 (slow-wave) sleep; *R,* REM sleep.

■ DETERMINATES OF SLEEP REGULATION

There are two processes that regulate the occurrence of sleep and the architecture of sleep periods. The homeostatic drive quantifies the physiologic need to sleep, and the circadian pacemaker ensures proper timing of the sleep process. Additionally, the circadian pacemaker is influential in the architecture and NREM/REM distribution sleep stages throughout the night (7).

Circadian Rhythms

The word "circadian" is derived from Latin roots *circa,* about, and *diem,* day. The term "circadian rhythm" refers to any behavior or physiologic process that is known to vary in a predictable pattern over a 24-hour period. This internal process is governed by a three-component mechanism. First, inputs such as light and activity help synchronize (entrain) to the environment. These inputs are called zeitgebers, which is German for "time giver." Next, information from zeitgebers is transferred to an internal clock, which acts as a pacemaker—setting the rate and timing of output pathways. Examples of these output pathways include lung function (8), sympathetic tone (9), and urine production (10), all of

which vary over a 24-hour period so that optimum performance occurs during the daytime.

The circadian pacemaker is focused in a hypothalamic structure, the suprachiasmatic nucleus (SCN). Genes that play a role in generating circadian rhythms were first identified in the SCN and subsequently identified in cells of every organ. There are an ever-increasing number of genes that participate in a negative feedback system to regulate the circadian processes. The mammalian circadian genes include *period* (*per 1, per 2,* and *per 3*), clock (*clock*), B-mal (*B-mal 1*), casein kinase 1 epsilon/1 delta (*CSNK1E* and *CSNK1D*), cryptochrome (*cry1* and *cry2*), and the nuclear hormone receptor *Rev-erba*. Less characterized components include *Timeless, Dec1, Dec2,* and *E4bp4*. These genes are highly conserved, and mutations appear to impact many human conditions, such as circadian rhythm disorders (advanced or delayed sleep phase), obesity, addiction, sleepiness, and bipolar disorder (11).

Sleep as a Two-process Model

The two-process model of sleep regulation has been used to explain the relationship between circadian rhythm regulation of sleep (process C) and the homeostatic drive to sleep (process S). Homeostasis is the process by which the body maintains stability. Thirst, hunger, and temperature are all processes that are carefully regulated to ensure optimum function. Sleep can be thought of as kin to these processes, and investigations in sleep deprivation have been the main tool for understanding the body's drive. Utilizing spectral analysis of EEG, slow-wave activity has been shown to be a significant hallmark of sleep debt. Because the debt is repaid by sleeping, slow-wave activity is reduced (12). To promote optimum sleep quality, maximum sleep debt should intersect with appropriate circadian time.

SLEEP AND THE PHYSIOLOGY OF THE IMMUNE SYSTEM

Sleep homeostasis and the circadian rhythm play an important role in maintaining optimal physiologic function of the immune system. A primary disruption in sleep will have an impact on the biology of the immune system, especially cell-mediated immunity. In addition, infections that challenge the host immune response will alter sleep patterns via effects on immune–neural connections.

The immune system shows diurnal variations at the cellular level, even under

physiologic conditions. Most mature leukocytes, with the exception of CD8$^+$ T cells, as well as hematopoietic stem and progenitor cells rise in circulation during sleep and decrease during wake (13). Sleep enhances T-cell proliferation, but suppresses natural killer (NK)-cell activity (14). Pro-inflammatory monocytes are suppressed at night, but conventional monocytes do not show a circadian pattern (15). Basal levels of tumor necrosis factor (TNF), interleukin 1 (IL-1), and their receptors have been found to have diurnal changes in the brain. Specifically, expression of TNF receptors fluctuates based on the sleep–wake cycle at the level of the SCN, the central circadian pacemaker (16). This finding highlights the complex and dynamic interplay of immune system components and the central nervous system, whereby changes in one affects the other and vice versa via myriad positive and negative feedback loops.

Some of the circadian influence on the immune system is mediated through the impact of melatonin. Melatonin is a hormone produced in the pineal gland as a result of dark exposure and in coordination with the central circadian clock. Binding of melatonin to specific receptors in antigen-activated T-helper cells results in an upregulation of cytokine production and immune function. Human studies demonstrate that melatonin favors a T_H1 cell response. The melatonin rhythm positively correlates with the rhythmicity of the T_H1 and T_H2 cell ratio. This seems to be most prominent when in the state of stress or immune suppression (17,18). Melatonin may play an additional role in enhancing immunity because melatonin is produced in T-lymphocytes and acts in intracrine, autocrine, and/or paracrine manner (19) (Table 42.1).

TABLE 42.1 CYTOKINES THAT INCREASE IN RESPONSE TO NOCTURNAL ELEVATION IN MELATONIN

IL-1

IL-2

IFN-γ

IL-6

IL-12

IFN-γ/IL-10 ratio	

A large part of the neuroimmune interaction is influenced by characteristic sleep regulatory substances (SRS), which are molecules that regulate changes in the immune system as a consequence of sleep. Specific criteria have been determined for defining a substance as SRS (20–22): (1) administration of the substance can increase or decrease sleep; (2) blocking the action of the substance or decreasing its production affects sleep; (3) the concentration of the substance or its receptor is regulated by the propensity of sleep; (4) disease states that increase sleep should alter the level of substance; and (5) the substance acts on known sleep regulatory pathways. IL-1, TNF, and growth hormone–releasing hormone are SRSs that alter NREM sleep, whereas SRSs prolactin and nitric oxide (NO) act on REM sleep (22).

Inflammatory cytokine release, including that of IL-1 and TNF, are part of an intricate cascade of events that occurs as a response to infection called the *acute-phase response* (APR). Excess sleep is a physiologic sign of the APR along with fever and anorexia. Studies show that the increase in sleep activity after infection is primarily mediated through an increase in NREM SWS. The cytokine milieu that is present after an infection is the likely mediator of this effect (15,23). Not all cytokines released as part of the APR enhance NREM sleep, but the balance is certainly shifted toward that direction (Table 42.2).

TABLE 42.2 IMPACT OF CYTOKINES ON GENERATION OF NONRAPID EYE MOVEMENT SLEEP

PROMOTERS	INHIBITORS
Low-dose IL-1β	IL-4
IL-2	IL-10
IL-6	IL-13
IL-8	TGF-β

IL-18	High-dose IL-1β
TNF-α	

IL-1, interleukin 1; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α.

Immunologic Impacts of Sleep Deprivation

Sleep loss is an ever-growing lifestyle pattern for today's population. The optimal duration of sleep is not known, but is generally estimated to be 7.5 to 8.5 hours per night. A literature definition for sleep deprivation is less than 6 to 7 hours per night (24). In 2013, the National Sleep Foundation reported their findings from the International Bedroom Poll which compared sleep times and habits among 25- to 55-year old adults in six countries (25). The study found greater than 50% of the people polled reported *not* getting enough sleep and that Americans and Japanese reported the least amount of sleep (averaging about 6.5 hours/night). In addition, a national 2010 survey reported that 30% of employed American adults were averaging less than 6 hours of sleep per night (26). This chronic partial sleep deprivation causes endocrine and immune dysregulation, which leads to weight gain (27–29), glucose intolerance (30), decreased cognitive function (24), and increased susceptibility to infection (31). Sleep deprivation may have an even greater impact in select populations who suffer from shift work sleep disorder, insomnia, alcoholism, and depression (15).

A major pathway for sleep deprivation's impact on the immune system is through increased levels of stress hormones. Cortisol and norepinephrine play an important role in cellular immunity, and they are found to be elevated after sleep deprivation (28,32). The effect on immunity depends on the severity of sleep deprivation. For example, one study showed T-helper cells and NK cells decreased after 40 hours of sleep deprivation, but the number of NK cells increased after 64 hours without sleep (33). Other data shows that functional activity of lymphocytes after sleep deprivation may be as important as the quantity. Decreased phagocytosis is seen after 72 hours, but the number of macrophages is increased. NK-cell lysis decreases with short periods of sleep deprivation, but increases with longer periods (34). Myeloid dendritic cell precursors that produce IL-12 are reduced, thereby resulting in a limit to antigen

presentation because of sleep reduction. Data on sleep deprivation effects on immunoglobulin levels, leukocytes, and other cytokines is mixed. More definitive studies are needed to arrive at a firm conclusion on how serum concentrations of immune factors change as a result of sleep loss. Current data is often contradictory depending on the amount of sleep loss and which immunity component is studied.

Overall, it is still likely that chronic sleep loss increases susceptibility to infection and decreases the ability to fight infection. Adults who perform variable shift work, which is associated with chronic sleep deprivation, have higher incidence of common infections compared to day work employees (35). In 2009, Cohen and colleagues (31) studied sleep efficiency (ratio of TST and total time in bed) and sleep length in 153 healthy men and women. After 14 days, the patients were inoculated with rhinovirus. Results showed that participants who slept less than 7 hours were about three times more likely to develop a cold than those with 8 or more hours of sleep. In the same vein, vaccine administration after sleep deprivation produces half the antibody titers compared vaccines given after normal sleep. This has been shown in humans after the flu shot (36) and the hepatitis A vaccine (37).

SLEEP DISORDERS IN THE ALLERGY PATIENT

Snoring

Until recently, it was commonly assumed that snoring was a benign annoyance, not associated with negative health outcomes; however, snoring is associated with daytime sleepiness (38), pregnancy-induced hypertension, and intrauterine growth retardation (39). In children, it is associated with poor school performance (40), parasomnias, and upper respiratory infections (41). Positive skin tests for common environmental allergens and prevalence of asthma and eczema have been correlated with an increased risk of snoring in pediatric populations (42,43).

Sleep Apnea

Definition

Sleep apnea is a broad diagnosis that includes many disorders of ventilation. Central sleep apnea describes respiratory pauses that occur because of failure of the central nervous system to trigger a respiratory effort. Alternatively, when a respiratory effort has been triggered, but a partial or complete obstruction of the upper airway prevents ventilation, obstructive sleep apnea (OSA) is diagnosed.

Sleep can also be disturbed by respiratory events during which an elevation of resistance through the upper airway impairs normal respiration requiring an increase in respiratory effort-related arousal (RERA) (44). The number of apneas plus hypopneas per hour is reported as the apnea hypopnea index (AHI); a number greater than or equal to five is abnormal. An AHI ≥ 5, plus daytime sleepiness, in an adult is consistent with the diagnosis of obstructive sleep syndrome. Although not routinely measured or reported in most sleep labs, 10 or more RERAs per hour are associated with daytime sleepiness and are known as the upper airway resistance syndrome (45).

Diagnosis

The prevalence of OSA is growing in the United States. The most recent data show 33.9% of men and 17.4% of women aged 30 to 70 years have OSA (46). Common clinical symptoms and physical findings suggestive of OSA are shown in Table 42.3. Diagnostic testing in one form or another is required to confirm suspicion for OSA and begin treatment. There are four types of diagnostic testing available for patients suspected of sleep-disordered breathing (Table 42.4), and OSA is the most common diagnosis (47–50). Although a full in-laboratory polysomnography (type I study) is the gold standard for diagnosing OSA, technologic advances in portable monitoring devices have increased the reliability of home sleep apnea testing (HSAT). Multiple studies have validated a portable, home-based strategy for diagnosing and treating OSA compared to in-laboratory testing (48,50,51). The most common HSAT device is a type III test and is an acceptable alternative for the diagnosis of OSA in patients with a high pretest probability for moderate-to-severe OSA. However, patients with certain concurrent neurologic and cardiopulmonary comorbidities are better suited for in-laboratory type I testing (Table 42.5) (50,51).

TABLE 42.3 SYMPTOMS AND PHYSICAL FINDINGS SUGGESTIVE OF OSA

SYMPTOMS OF OSA	PHYSICAL EXAM FINDINGS IN OSA
Excessive daytime sleepiness	Obesity (BMI > 30 kg/m^2)
Loud snoring	Neck circumference > 16 inches in women, >17 inches in men
Choking/gasping during sleep	Modified Mallampati score 3 or 4

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Witnessed apneas by bed partner	Retrognathia or micrognathia
Morning headaches	Tonsillary hypertrophy
Nonrestorative sleep	Nasal obstruction including polyps, septal deviation, chronic congestion
Sleep fragmentation	Macroglossia

BMI, body mass index; OSA, obstructive sleep apnea.

TABLE 42.4 TYPES OF DIAGNOSTIC SLEEP TESTING

TYPE	DEFINITION
I	Full, in-lab PSG with a minimum of seven channels recorded, including EEG, EOG, EMG, ECG/HR, airflow, effort, and SaO_2
II	Full PSG with similar parameters as above performed unattended outside the sleep lab. This is a portable study
III	A portable study with a minimum of four channels, including airflow, effort, heart rate, and SaO_2
IV	A portable study with one or two channels, including nocturnal oximetry or airflow.

ECG, electrocardiography; EEG, electroencephalopgraphy; EMG, electromyography; EOG, electrooculography; HR, heart rate; PSG, polysomnography; Sao_2, oxygen saturation.

Treatment

There are multiple treatment modalities available for patients diagnosed with OSA, including medical, surgical, and behavioral options. They should be

approached with respect to the patient's personal preferences, as well as anatomy and comorbidities. In general, positive airway pressure (PAP) therapy, which acts as a pneumatic splint in the airway, is the treatment of choice for patients with mild, moderate, or severe OSA (52). Continuous positive airway pressure (CPAP) is the most well-studied therapy for OSA and has been shown to have multiple health benefits, including decrease in respiratory events during sleep, improvement in objective and subjective sleepiness, improved neurocognitive function, decreased systemic blood pressure, and overall quality of life measures (53–55).

TABLE 42.5 INDICATIONS FOR A FULL CHANNEL, ATTENDED, IN-LABORATORY SLEEP STUDY

Moderate-to-severe pulmonary disease such as COPD or asthma that requires home oxygen or daytime hypercapnia with PaO_2 < 60 mm Hg or $PaCO_2$ > 45 mm Hg

Neuromuscular disease or stroke with residual respiratory effects

Epilepsy

Congestive heart failure (NYHA class III or IV or LVEF < 45%)

Super obesity (BMI > 45)

Obesity hypoventilation syndrome (BMI > 35 and $PaCO_2$ > 45 mm Hg)

Uncontrolled psychiatric disturbance

BMI, body mass index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association heart failure classification scheme; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen.

Traditionally, the initiation of CPAP therapy is preceded by a CPAP titration study in a sleep laboratory, where the technician helps determine the minimum pressure at which the patient's sleep-disordered breathing is decreased below the acceptable amount. In contrast, auto-titrating positive airway pressure (APAP) therapy eliminates the need for this overnight stay. APAP devices, in contrast to

fixed pressure devices like CPAP, titrate the level of PAP in response to changes in airflow, snoring, and pressures in the circuit. APAP therapy shows similar adherence rates and effectiveness in eliminating respiratory events and sleepiness when compared to CPAP (56,57). APAP is a suitable treatment strategy for uncomplicated OSA.

CPAP and the Allergy Patient

CPAP therapy has been associated with poor compliance in the allergy patient. Nasal complaints often contribute to noncompliance. Unfortunately, nasal evaluation prior to CPAP initiation may not be helpful in these OSA patients. Subclinical nasal inflammation cannot be identified from clinical assessment or rhinomanometry. Nasal neutrophil counts before treatment may predict noncompliance because of nasal symptoms. There is a correlation between neutrophil counts and nasal bacterial scores, both before and after treatment with nasal CPAP (58). In an animal model, free of bacteria, the application of CPAP can increase nasal inflammation. Macrophage inflammatory protein-2 is significantly overexpressed after only 3 hours of CPAP therapy. No significant changes were found in TNF-α, nerve growth factor, or tachykinin-1 receptor (59). Heated humidity can improve both CPAP compliance and peak nasal inspiratory flow in CPAP users who have nasal symptoms limiting therapy. The heated humidity has been successful even when nasal steroids and antihistamines have failed (60). Patients with a significant mouth leak may have nasal obstruction, ongoing apnea, or a poorly fitting mask (61). Although bacterial colonization, humidity, and mouth leak have been associated with nasal complaints and CPAP noncompliance, there have not been any trials evaluating specific interventions to address these issues. Table 42.6 contains some commonly used strategies to resolve these issues.

ALLERGY, ASTHMA, RHINITIS, AND SLEEP-DISORDERED BREATHING

Allergic conditions have an intricate relationship with OSA. The most common cause of OSA in children is related to structural abnormalities, such as tonsil or adenoid hypertrophy. Recently, Ni et al. reported that OSA in children was associated with a dysregulation of T cells, specifically T_H17 cells and Treg cells. T_H17 cells increase IL-17 production that is associated in the development of autoimmunity and allergic reactions. Their study found that an increase in the T_H17 to Treg ratio in children was associated with OSA, larger adenoid size, and increased incidence of allergic rhinitis (62). Previously, a large retrospective

study had shown that patients with a diagnosis of chronic rhinosinusitis had a higher prevalence of sleep apnea (63). Additionally, radioallergosorbent testing is positive in 40% of children that snore and 57% of children with sleep apnea (64). Occupational allergy to guar gum has been reported to cause both rhinitis and OSA, and both complications resolved after exposure ended (65).

TABLE 42.6 SUGGESTED STRATEGIES TO ADDRESS SOME OF THE PUBLISHED CAUSES OF NASAL OBSTRUCTION FROM CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)

STRATEGIES TO IMPROVE CPAP COMPLIANCE BY REDUCING NASAL SYMPTOMS

1. Increase humidity
    a. Increase temperature on the humidifier
    b. Add insulation to the tubing (socks, fabric, or run the tubing under blankets)
    c. Change to a device with heated tubing

2. Reduce mouth breathing
    a. Add a chin strap
    b. Change to a full face mask
    c. Consider retitration, if mouth opening may be due to ongoing apnea

3. Reduce bacterial colonization
    a. Encourage proper care
        i. Use of distilled water
        ii. Frequent cleaning with soap or vinegar
    b. Nasal saline lavage

OSA may predate allergic disease in the patient. Nasal inflammation, as assessed by polymorphonuclear cells, bradykinin, and vasoactive intestinal peptide, is increased in nasal samples of patients with OSA who do not have allergic rhinitis (66). Mechanical nasal obstruction itself can induce nocturnal apneic events in individuals without underlying OSA (67). There is a twofold

increased risk of snoring in women with asthma (68).

TABLE 42.7 NONPHARMACOLOGIC THERAPY FOR INSOMNIA

SLEEP HYGIENE

1. Eliminate caffeine, alcohol, and tobacco
2. Quiet, dark, comfortable bedroom
3. Regular sleep and rise times
4. After exercising, allow several hours before bedtime

SOMATIC RELAXATION

1. Progressive muscle relaxation
2. Cognitive relaxation and positive imagery

BEHAVIORAL THERAPIES

1. Do not go to bed unless sleepy
2. The bedroom should be used for sleep and sex only
3. If lying in bed awake unable to sleep after 20 min, get out of bed until sleepy
4. Avoid napping

OSA can complicate the management of asthma. By self-report, in a large nonselected population, asthma is associated with a 2.5-time increase in the prevalence of OSA, and patients with asthma and OSA may have more nocturnal hypoxemia than patients with OSA alone (69). The prevalence of sleepiness, snoring, and apnea is significantly higher in patients with asthma (70), and recently asthma was associated with an increased risk of new-onset OSA (71). Treatment of OSA can improve control of asthma symptoms (72,73) and reduce airway hyper-reactivity as measured by methacholine responsiveness (74). One potential reason that OSA may worsen asthma is that OSA is associated with airway inflammation. Exhaled pentane and nitric oxide levels are increased after deep sleep in patients with moderate-to-severe OSA (75).

THE ALLERGY PATIENT AND INSOMNIA

Although sleep disturbance from asthma has classically been associated with daytime sleepiness, epidemiologic studies have found insomnia may be more common. In one study of patients with active asthma, 52% reported insomnia,

whereas only 22% reported daytime sleepiness. Even when symptom free, 28% of asthmatics reported insomnia (75). Many factors, such as medication side effects and psychologic factors, may contribute to the persistence of insomnia. Medications used to treat asthma, such as theophylline, pseudoephedrine, and corticosteroids, are associated with insomnia, and when combined, the effect is magnified (76,77). Exploration of alternative medications or dosing regiments that avoid dosing late in the day should be first-line management. Psychophysiologic factors may perpetuate this insomnia. The hallmarks of psychophysiologic insomnia include chronic insomnia lasting over 1 month, and although there may have been an initial trigger, the insomnia symptoms persist even though the inciting event has been resolved. These patients have anxiety about going to bed, but are able to fall asleep at other locations and times. Improvements in sleep hygiene along with behavioral and relaxation therapy may be helpful (Table 42.7) (78). Short-term use of short-acting benzodiazapines can be a helpful adjunct but should be initiated with caution in the setting of theophylline that speeds their elimination (79).

SUMMARY

Sleep is a process that occurs as the result of the interaction between circadian rhythms and sleep homeostasis. An adequate amount of quality sleep is required for health and well-being. Complete care of the allergy patient requires attention to the commonly coexistent sleep disorders of asthma and rhinitis that impact the quality of life of both children and adults. Taking a routine sleep history that allows a patient to discuss issues of daytime sleepiness, snoring, apnea, or insomnia will allow health care providers to coordinate care for these important issues.

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Management of the Psychologically Complicated Patient

MICHAEL S. ZIFFRA AND JACKIE K. GOLLAN

Psychiatric and psychosocial issues complicate management of medical illness, with allergic diseases being no exception. The presence of concurrent psychiatric diagnoses or more enduring maladaptive personality traits can interfere with the physician–patient relationship and patient adherence to medical care. Even normal, expected reactions to acute and chronic medical illness can create distress and hinder care.

Who is the *psychologically* complicated patient? This term can apply to patients with a significant psychiatric illness, such as depression, bipolar disorder, or anxiety disorder. This term may also refer to individuals with problems such as substance abuse, personality disorders, and nonadherence with medical treatment. Physicians treating such patients must invest greater-than-usual amounts of time and effort to optimally manage their medical and psychiatric issues.

Balancing concurrent psychiatric and allergic diseases is challenging for patients and their health care providers. Many physicians feel they do not have sufficient experience and skill to manage these types of issues, potentially making them feel powerless or guilty about their inability to help the patient. It is essential, therefore, that all physicians develop a basic understanding of major psychiatric illnesses and clinically relevant psychosocial issues. Being able to work with psychiatrically complicated patients in an empathic manner not only leads to more compassionate care but also enhances effective management of the primary medical diagnosis.

This chapter highlights the clinical advances in treating individuals with allergic disorders and comorbid psychiatric conditions, with discussion of common psychiatric disorders, treatment approaches, and clinical challenges requiring attention to promote clinical effectiveness. Common psychiatric

diagnoses and other psychosocial barriers to care are first outlined, followed by a discussion of effective, evidence-based treatments and their practical administration.

MOOD DISORDERS

According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (1), a major depressive episode is defined as a period lasting 2 weeks or more of predominantly depressed mood, accompanied by other symptoms (see Table 43.1). The diagnosis of major depressive disorder (MDD) is given to an individual who has had one or more major depressive episodes (and does not meet diagnostic criteria for bipolar disorder). MDD is considered a devastating and recurrent disease, and depressive disorders were found to be the second leading cause of worldwide disability in 2010 (2). Up to 20% of the general population is expected to experience major depression at least once during their lifetime. These statistics may underestimate the true prevalence of depression, because symptom complaints are often disregarded or misdiagnosed, particularly among primary care and geriatric populations (3). Also, depression recurs over the life span (4). Specifically, the Agency for Health Care Policy and Research has noted that the risk of recurrence increases exponentially with each successive episode. Even after treatment, 40% of patients with a history of three or more depressive episodes are likely to relapse within 7 weeks after recovery (5). Given the prevalence and chronicity of depression, innumerable people face the prospect of a lifetime struggle with depression.

TABLE 43.1 SYMPTOMS OF MAJOR DEPRESSION

- Depressed mood
- Loss of interest/pleasure
- Changes in appetite and weight
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue
- Impaired concentration and/or indecisiveness
- Feelings of worthlessness, shame, or guilt
- Thoughts about death or suicide

Adapted from American Psychiatric Association. *Diagnostic and Statistical Manual of*

MDD is more prevalent among individuals with many types of chronic illness, including hypertension, congestive heart failure, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, stroke, and end-stage renal disease. Depression in chronic illness has been associated with greater symptom burden and functional impairment, higher rates of morbidity and mortality, and decreased treatment adherence. It also results in decreased productivity and greater health resource utilization (6–8).

A significant association between depression and allergic disorders has been observed. Depressed patients have higher rates of atopic illness than nondepressed individuals (9–12). Meanwhile, allergic disease may increase the risk for depression threefold (9). Psychiatric disorders are more prevalent in patients with asthma and other allergic diseases. Also, evidence has shown a correlation between the severity of depressive symptoms and that of allergic symptoms (10).

The reasons for this relationship are not completely understood and are likely very complex. Depression is associated with changes in functioning of the immune system, which could predispose individuals to atopic illness. Cytokines, leukotrienes, and other substances released during allergic reactions may have effects on neurotransmitter activity involved in the regulation of mood. Dysfunction of the hypothalamic-pituitary-adrenal axis and alterations in fatty acid metabolism are believed to occur in both depression and allergic disease (9–12). Interestingly, twin studies have suggested that the two types of illness may have a common genetic cause (9–12). Thus, the higher prevalence of depression in patients with atopic illnesses, as well as its potential effects on the severity of allergic symptoms, underscores the need for allergist-immunologists to recognize depressive disorders in their patients to ensure that they receive appropriate treatment (13).

Bipolar disorder is another serious mood disorder associated with significant disability. It is characterized by the presence of both major depressive episodes and episodes of mania or hypomania. Mania is defined as a period of excessively elevated or excited mood, typically accompanied by increased energy, anger, irritability, and impulsivity. Key signs and symptoms of mania are listed in Table 43.2. Hypomanic episodes are characterized by these same symptoms, but they are less severe and shorter in duration (1).

TABLE 43.2 SYMPTOMS OF MANIA

Though mood disorders can be quite disabling, they are also treatable. For this reason, it is important that treatment be initiated as soon as the disorder is identified, and sustained until remission is achieved. Increasingly, primary care physicians and other nonpsychiatrists are treating depression in their patients, typically by prescribing antidepressant medications (14). This practice is reasonable for patients who are reluctant to accept a referral to a mental health specialist and whose depression is not severe.

Patients with symptoms indicative of severe depression are best referred to a psychiatrist. Such symptoms include active suicidal ideation, psychotic symptoms such as hallucinations and delusions, prominent agitation or volatility, and significant decline in functioning. Other situations that warrant psychiatric consultation include treatment-resistant depression (which can be defined as failure to adequately respond to three or more antidepressants), suspicion for bipolar disorder, complicated psychiatric comorbidity, complex psychopharmacologic regimens, and concomitant substance abuse (15).

Psychotherapy is beneficial in the treatment of mood disorders, and it can be effective as the sole treatment for depressive episodes of mild-to-moderate severity. There are empiric data supporting the use of some types of psychotherapy, including cognitive-behavioral therapy and interpersonal therapy, in the treatment of depression. More severe depressive episodes typically require a combination of concurrent psychotherapy and medication (16).

Bipolar disorder is best managed by mental health specialists, given the complex nature of the disease and the medications used to treat it. A variety of pharmacologic agents are used to treat bipolar disorder, including lithium, mood-stabilizing anticonvulsants, antipsychotics, and antianxiety medications.

Psychotherapy is also a key component of bipolar disorder treatment (17).

◼ ANXIETY DISORDERS

Anxiety disorders are also frequently encountered in general and specialty medical practices. Like depression, anxiety disorders are highly comorbid with many types of medical illness, and they are associated with higher rates of morbidity and mortality, health care utilization, and functional disability (18). Several distinct anxiety disorders have been described in the medical literature. Among these are panic disorder, generalized anxiety disorder (GAD), agoraphobia, social phobia, and specific phobia. Related disorders that typically have anxiety as a key component include obsessive-compulsive disorder (OCD), characterized by recurrent, intrusive thoughts, and/or rituals and repetitive behaviors; and posttraumatic stress disorder (PTSD), in which individuals experience a number of anxiety-related symptoms following a serious trauma (1).

Both panic disorder and GAD merit particular mention, given their high prevalence and the frequency with which they are encountered by nonpsychiatrists. A panic attack is an episode of intense anxiety that develops and resolves over a brief period of time and is accompanied by a number of somatic and psychologic symptoms. These symptoms can include palpitations, chest pain, shortness of breath, nausea, trembling, dizziness, and paresthesias. Because panic attacks are characterized by intense fear and uncomfortable physical symptoms, individuals in the midst of an attack may worry that they are having a heart attack or even close to dying. This may lead to their seeking medical attention (19).

Panic attacks can occur as part of many anxiety disorders. Panic disorder is specifically defined as a pattern of recurrent, unexpected panic attacks. This is accompanied by at least 1 month of the patient worrying about future attacks or changing his or her behavior because of the attacks. Panic attacks can be accompanied by agoraphobia, which is a fear of places in which escape or help might not be available if an attack were to occur (such as being on a bus or plane, or in a large crowd).

GAD, meanwhile, is characterized by worry about multiple topics—such as work, family, and money—that is excessive and hard to control. This worry is accompanied by at least three additional physical or psychologic symptoms, which include fatigue, sleep disturbance, muscle tension, restlessness, difficulty concentrating, and irritability. Just as with panic disorder, the presence of

somatic symptoms in GAD may prompt patients to seek medical attention (20).

As is the case with depression, anxiety is often treated directly by patients' primary care physicians, and sometimes, this can be appropriate in cases of mild-to-moderate anxiety (21). Most antidepressants are quite effective for treating anxiety (bupropion being a notable exception), and they actually are first-line agents for most anxiety disorders. Benzodiazepines are also commonly used, often in conjunction with an antidepressant (22).

Many patients with anxiety disorders, however, require treatment by a mental health specialist. Examples include patients with more serious symptoms, such as patients whose fear of panic attacks is so severe that they rarely leave their home or avoid important activities or obligations. Other situations that would necessitate psychiatric referrals include treatment-resistant anxiety, comorbid psychiatric illness, and concomitant substance abuse. Also, OCD and PTSD are two particularly challenging diagnoses that are best treated by mental health specialists.

Psychotherapy also plays a prominent role in the management of anxiety disorders. Many anxiety disorders of mild-to-moderate severity are very amenable to treatment with psychotherapy alone. Severe or treatment-resistant anxiety disorders are often best managed through a combination of medication and psychotherapy (22).

Of note, a significant correlation between anxiety and allergic disorders has been described in the literature (23–26). Anxiety is actually the most common psychiatric diagnosis in patients with allergies. The association between panic disorder and atopic illnesses, especially asthma, is particularly strong (23). Furthermore, in a series of male twins who were Vietnam War veterans, compared to subjects without asthma, the subjects with asthma had higher symptom scores on an instrument used to measure severity of PTSD. In veterans with mild PTSD, the prevalence of asthma was 4% compared to 7% in those veterans who had the highest scores on the PTSD instrument (26).

The reason for this correlation is unclear, and the causation may actually be bidirectional. Both acute allergic events and chronic allergic disease can be stressful, contributing to anxiety. Via classic conditioning, patients can become excessively fearful of those stimuli that cause allergic reactions. Meanwhile, anxiety can often precede (and thus possibly precipitate) allergic exacerbations, and allergic patients with anxiety have more severe physical complaints and use more medical care (24). Interestingly, there is evidence that abnormalities in the brain that contribute to anxiety may also predispose to allergic disease by

disrupting the central nervous system's (CNS) regulation of the immune system (23). From these data, therefore, it seems reasonable to conclude that optimizing management of anxiety symptoms can improve allergic symptoms and vice versa.

■ SOMATIZATION AND HYPOCHONDRIASIS

The group of disorders historically described as somatoform disorders are characterized by patients' preoccupation with physical symptoms and medical illness that cannot be fully explained by a general medical condition. Because of this, these disorders are frequently encountered by nonpsychiatrists, although they may not initially be recognized as such. Two common manifestations of somatoform illness are somatization and hypochondriasis. Although both somatization disorder and hypochondriasis were previously recognized as distinct diagnoses, with DSM-5, there have been changes in how these illnesses are construed and classified. Under DSM-5, most individuals who previously would have been diagnosed with somatization disorder and hypochondriasis would now receive a diagnosis of somatic symptom disorder. Somatic symptom disorder consists of somatic symptoms that are distressing or disruptive, accompanied by one of the following: unreasonable thoughts about the seriousness of the symptoms, persistently high anxiety about the symptoms, or excessive time and energy devoted to the symptoms (1). Although somatization disorder and hypochondriasis are no longer officially recognized as distinct diagnoses, there are no significant changes in how these phenomena present and are managed.

Somatization occurs when a patient experiences somatic complaints that have no direct physiologic cause. Psychologic factors are assumed to be involved in the development and maintenance of the physical symptoms; however, the patient typically is unaware of this, and the symptoms are not consciously manufactured or feigned (27).

Patients with hypochondriasis also experience somatic complaints that are concerning to them. However, in contrast with somatization, in hypochondriasis, these symptoms do in fact have some physiologic basis. Their "symptoms" are normal bodily functions and reactions that are misperceived as being signs of a serious medical illness. Hypochondriacal patients can be plagued with worry about their possibly having a dangerous disease. Even when their health care providers produce evidence of their good health, they are rarely reassured (28,29).

Patients with somatization and hypochondriasis usually seek medical attention to diagnose and treat their unexplained symptoms. They are typically concerned about their perceived illness, and they may become increasingly frustrated because physical exams and laboratory studies fail to reveal any identifiable medical condition. These patients can often end up seeing multiple specialists and receiving numerous expensive procedures. This experience can be just as frustrating for the physician. Feelings of incompetence, failure, and guilt can be evoked because of the inability to treat the patient's complaints and allay their worries. In cases in which the patient demands multiple visits, referrals, and studies, the physician may become angry and resentful toward the patient.

Notably, before a diagnosis of somatization or hypochondriasis is issued, a thorough investigation should occur to rule out organic medical illness. The medical literature is replete with stories of patients who were initially dismissed as being a "somatizer" or "hypochondriac" and later were found to have a genuine biologic disease. Unfortunately, patients with a history of comorbid psychiatric illness in particular can be too quickly judged to have psychosomatic illness. Though a "million-dollar workup" is generally not indicated for every patient with unexplained or unusual complaints, a reasonable effort must be made to rule out likely medical causes for the patient's symptoms.

Clinical management of somatization and hypochondriasis is very similar (27–29). Mental health referral is typically helpful. Liaison with mental health specialists can also help the primary care providers appropriately understand and manage their patients. Also, because depression and anxiety disorders are common in patients with somatoform disorders, a psychiatrist can evaluate for, and treat, any such comorbid psychiatric illnesses. Medication helps to manage comorbid depression and anxiety, though there is less evidence that it treats somatoform disorders directly. Psychotherapy appears to be a more effective modality for treating somatization and hypochondriasis. Evidence supports the use of psychotherapeutic interventions that teach patients to cope with their physical symptoms and medical concerns in a less maladaptive manner.

Some patients may resist referral to mental health specialists, for a variety of reasons. They may see such a referral as a message that their primary treater is abandoning them, or considering their problems to be "all in their heads." The physician must reassure the patient that neither of these is true. Patients may be more amenable to a mental health referral if it is presented as a supplement to their existing medical treatment, or as a treatment to reduce "stress" that may be impacting their physical complaints.

Even when psychiatric consultation is obtained, it is still necessary for the referring medical health care provider to continue to meet with the patient. In fact, denying further visits may produce a sense of abandonment, further exacerbating patients' anxiety, ultimately leading them to seek out regular medical care again. It is recommended that frequent, brief "check-in" appointments be scheduled, regardless of how the patient is feeling. Such an arrangement can be reassuring to patients, even though no additional medical investigation or treatment is being performed. "As-needed" visits and telephone calls should be minimized, because they can reinforce patients' maladaptive behaviors.

SUBSTANCE USE DISORDERS

Substance use disorders involve the overuse of, and reliance on, a drug or chemical that produces specific responses that are deleterious to the well-being of the individual or others. These conditions are typically characterized by a pattern of use of a substance (medication, alcohol, drug, or toxin) that generates recurrent problems in social, occupational, academic, and personal functioning. Although overuse and dependence are sometimes difficult to determine, DSM-5 diagnostic criteria clarify signs of problematic use. Examples include physiologic reliance (exhibited by tolerance and withdrawal), continued substance use despite knowledge of its causing physiologic and psychologic problems, and escalating use with unsuccessful efforts to cut down (1). Patients with addiction problems may be less likely to adhere to recommended medical treatments because of the large amount of time spent using substances and recovering from their effects. They may also avoid meeting with their physicians, owing to feelings of guilt or shame, or out of fears of their addictions being discovered.

When physicians learn that a patient is actively abusing drugs or alcohol, they must remember that the patient is not necessarily ready to seek treatment for it, even if the substance use is voluntarily disclosed. The patient's readiness for change must be gauged in a nonconfrontational manner, using questions that promote motivation to change (30). If the patient expresses reluctance to seek treatment, the physician should empathically explore his or her resistance. Questioning the patient aggressively and making ultimatums are likely to be counterproductive. Pointing out objective facts about the adverse consequences of the patient's substance use (such as medical problems and interpersonal difficulties) can help give him or her motivation to change. Often this process requires several conversations over multiple visits.

Once the patient expresses a desire to change, the physician must help him or her establish treatment in an appropriate setting. Patients who are at risk for complicated withdrawal—which includes those who are medically compromised and those withdrawing from alcohol, sedatives, or opiates—may need inpatient hospitalization for detoxification. Also, patients with significant active psychiatric issues (such as severe depression or suicidality) may require admission to an inpatient psychiatric unit. Other levels of care include residential treatment settings, day hospital programs, and outpatient treatment (31,32).

Consultation with a psychiatrist or psychologist, ideally one who specializes in addictions, may help the primary care physician refer the patient to an appropriate treatment setting. These professionals can also help to diagnose and manage any comorbid psychiatric illnesses that may be present. Ongoing mental health treatment will be necessary after any acute intervention, and participation in groups that help to maintain sobriety (such as Alcoholics Anonymous and other 12-step groups) is strongly encouraged.

PERSONALITY DISORDERS

The DSM-5 defines a personality disorder as "an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture," resulting in distress and social interference (1). Identifying personality disorders is particularly meaningful for medical staff working with allergy patients, because these mental disorders influence cognition, affectivity, social functioning, and impulse control. The 10 classified personality disorders in the DSM-5 are grouped into three clusters based on their prominent characteristics: cluster A, the odd or eccentric (paranoid, schizoid, and schizotypal); cluster B, the dramatic, emotional, or erratic (antisocial, borderline, histrionic, and narcissistic); and cluster C, the anxious or fearful (avoidant, dependent, and obsessive-compulsive). The prevalence of personality disorders in the general population is 10% to 12%, although many more individuals exhibit maladaptive personality traits insufficient to merit a diagnosis of a personality disorder. These disorders are highly associated with other psychiatric illnesses, including depression, anxiety, and substance abuse and dependence; they are also associated with significant medical comorbidity and higher health care utilization (33,34).

We direct the interested reader to several excellent reviews for helpful treatment and management strategies for individuals with personality disorders (35–37). Generally, health care providers should initially construct and evaluate

a differential diagnosis to ensure that patients' symptoms are unrelated to use of substances or medications, CNS disorders, or other medical problems. Then, physicians should consider referral for their patients to meet with a psychologist or psychiatrist to generate a tailored treatment plan for careful and effective management of symptoms concurrent with the treatment of atopic conditions. This is essential when health care providers encounter difficulty sustaining their usual empathic neutrality and involvement; professional and personal boundaries; and interpersonal demeanor with patients and their families.

NONADHERENCE

Nonadherence is a significant problem in the management of allergic diseases. For example, in patients with asthma, adherence to pharmacologic treatment has been found to be low, with many studies reporting adherence rates at or below 50% (38,39). Similarly, poor adherence rates have been found in patients with allergic rhinitis (40). Table 43.3 lists common problems that contribute to nonadherence and how they can be addressed (39–43). Many barriers to adherence are connected to problems in the delivery of care by individual physicians or the health care system as a whole. Other barriers relate to patient factors, such as treatment resistance.

TABLE 43.3 COMMON CAUSES OF AND REMEDIES FOR NONADHERENCE

PROBLEM	POSSIBLE SOLUTIONS
Complex medication regimen	Reduce number of medications taken.
	Switch to once-daily dosing.
	Provide clearly written instructions.
Patient forgetfulness	Provide written and telephone reminders.
	Instruct patient to use a pillbox.
	Use more convenient packaging (such as prepared blister packs).
Medication side effects	Switch to drug with fewer side effects.
	Add agents to treat side effects.
	Inquire about and address excessive worries about potential side effects.

Cost concerns	Switch to less expensive agent.
	Connect patient with financial assistance programs.
Language barriers	Use interpreter during visits.
	Provide written information in patient's primary language.
Poor understanding of disease and/or need for medication	Actively inquire about and explore patients' beliefs about their illness.
	Address patients' denial of severity of illness and/or concern about taking medication. Provide written educational material.
Poor relationship with physician	Engage actively with patients (ask/answer questions, provide feedback).
	Ensure accessibility between visits.
	Increase duration and/or frequency of visits.
	Have patient see same physician at each visit.
Patients' difficulty in making or keeping follow-up appointments	Use written/phone reminders.
	Assist with transportation, parking.
	Offer convenient clinic hours.
	Minimize long waits for visits.

Treatment resistance is characterized by dimensions related to patients (e.g., behavior, thinking, and social interaction) that interfere with their abilities to utilize the treatment and learn how to handle their disease and its implications. This may manifest itself as premature termination of medical care, noncompliance with the treatment regimen, a slow learning curve, or an unequal or imbalanced therapeutic alliance. Behavioral interventions include providing psychoeducation (to eliminate treatment myths and increase realistic expectations), evaluating medication compliance between sessions, slowly integrating the assigned treatment regimen (which reduces the patient's sense of helplessness), and increasing contingencies via providing praising statements after specific behaviors. Additional strategies to address resistance include

organizing the session using an agenda, making sure that the patient and physician are working collaboratively (with consistent provision of empathy, collaboration, and validation), identifying and modifying self-limiting beliefs that interfere with treatment, and responding to patients' pathologic strategies to elicit validation (such as escalating the intensity of symptom complaints or devaluing the medical provider).

■ PHARMACOLOGIC INTERVENTIONS

As noted previously, antidepressants and other psychoactive medications are commonly prescribed by physicians with minimal psychiatric training. Therefore, it is essential for clinicians to be familiar with the basic principles behind these agents' use (44). The selective serotonin reuptake inhibitors (SSRIs) are among the most commonly prescribed antidepressants. This class of antidepressants, which includes fluoxetine, paroxetine, sertraline, citalopram, and escitalopram, is effective in treating depression and anxiety and has a favorable side effect profile. The SSRIs tend to not cause serious drug interactions, though fluoxetine, paroxetine, and sertraline have the potential to cause some interactions via action at the hepatic P450 system. Medications in the class known as serotonin-norepinephrine reuptake inhibitors (SNRIs)—which include venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran—are also commonly prescribed. Both SSRIs and SNRIs have several properties in common, although the latter tend to be more stimulating (and thus can be more problematic for patients who are very anxious).

Other newer antidepressants commonly used include bupropion, mirtazapine, vortioxetine, and vilazodone. Like the SSRIs and SNRIs, they are all considered to be efficacious and relatively safe agents, though each has a unique mechanism of action and side effect profile.

Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are older classes of antidepressants that are used less frequently, although they can be effective medications in patients with treatment-resistant depression. The primary reason for their less frequent use is their potential to cause more severe side effects and more dangerous drug interactions. Thus, these agents are best prescribed by clinicians who are familiar with their use and aware of the potential for adverse events (45–47).

After prescribing an antidepressant, it is important to schedule regular follow-up. This step is necessary to ensure that patients are responding to treatment and to make any necessary adjustments. Regular follow-up also enables the

physician to quickly identify and address any adverse side effects. For example, antidepressants can trigger agitation or mania in patients with undiagnosed bipolar disorder (48). Therefore, it is crucial to screen for bipolar disorder before prescribing an antidepressant.

Regarding the use of these medications in patients with atopic illness, most of them are safe and well tolerated. One exception is MAOIs. In conjunction with the administration of sympathomimetics like epinephrine, hypertensive crisis can occur. Serotonin syndrome is also possible when MAOIs are combined with agents that have serotonergic properties, which include many nonantidepressants (46). Before prescribing any medication, the potential for drug interactions must be considered. In those who are significantly medically compromised or are taking several other medications, the TCAs and MAOIs may be best avoided.

Benzodiazepines are commonly used antianxiety agents, and unlike antidepressants, they have the benefit of producing immediate effect. Because of the risk for tolerance and dependence, these medications should be used judiciously. Using the smallest amount necessary for the shortest amount of time necessary is a wise practice (22).

Although the most commonly prescribed psychoactive medications are unlikely to exacerbate allergic diseases, several medications used to treat allergic disorders can worsen psychiatric disorders. Allergists thus need to be aware of these potential reactions in patients with comorbid psychiatric illness.

Corticosteroids are particularly notorious for the potential to cause neuropsychiatric side effects. Such effects can manifest in multiple ways, including mania, depression, memory impairment, delirium, and psychosis. The risk for these adverse events is dose dependent, with those patients taking less than 40 mg/day at low risk and those receiving 80 mg/day at significant risk. The most effective management of these side effects is to lower the dose of the corticosteroid, or discontinue it completely. Because this approach may not be feasible, addition of a psychoactive medication (the particular medication depending on the specific type of side effect) can be helpful (49,50).

A potential link between suicide and leukotriene-modifying agents (including montelukast, zafirlukast, and zileuton) has been observed. In 2009, the U.S. Food and Drug Administration issued a warning about risk for suicide and other neuropsychiatric events with these agents, also requiring the drugs' manufacturers to include a precaution in the drug labeling. However, the evidence is limited with respect to causality and the possible mechanism of action by which these medications would cause neuropsychiatric side effects. It

has been recommended that patients prescribed these medications be closely monitored for suicide risk and changes in mood (51).

β-Adrenergic agonists used in the treatment of asthma can produce several physiologic effects shared with panic attacks, including elevated heart rate, palpitations, tremor, and CNS stimulation. Thus, among patients prescribed such medications, those with preexisting panic attacks may experience worsened anxiety symptoms, and those without may report panic-like episodes. If avoiding β agonists is impractical, patients may benefit from a mental health referral to help manage their anxiety symptoms (52).

Both prescription and over-the-counter H_1 antihistamines are used to treat a variety of illnesses and are in general quite safe. Because of the potential for sedation, primarily from first-generation H_1 antihistamines, they should be used with caution when combined with sedating psychoactive medications, such as benzodiazepines. In addition, first-generation H_1 antihistamines have the potential to cause delirium, which is generally attributable to their anticholinergic effects. Thus, these medications should be used judiciously in older patients and others whose illnesses and pharmacologic regimens may predispose them to delirium. Second- and third-generation H_1 antihistamines that do not cross the blood–brain barrier are much less likely to produce these adverse events (52).

COGNITIVE AND BEHAVIORAL THEORIES AND THERAPIES

Evidence-based psychotherapies, specifically cognitive and behavioral therapies, assist in the management and treatment of psychiatric issues among patients presenting with allergic conditions. These approaches underwent intense empirical scrutiny in the 1980s, and the application of these models is producing a variety of effective psychosocial treatments (e.g., psychologic therapies with demonstrated efficacy in comparison to pill placebos or active medications). Such empirically validated approaches to psychotherapy are exemplified by cutting-edge therapies for depression, anxiety disorders, eating disorders, personality disorders, and substance use disorders (53).

Behavioral psychotherapy focuses on changing behavior by helping individuals "unlearn" previously acquired associations that linked stimuli and maladaptive behaviors. This type of therapy is especially indicated for the treatment of anxiety disorders. Effective treatment of anxiety includes, initially,

anxiety management techniques, including breathing retraining and progressive muscle relaxation, followed by exposure and response prevention (e.g., stepwise introduction to feared situations that rely on habituation and systematic desensitization). Behavioral therapy is also used to modify behaviors by conditioning them with negative or positive feedback. The targeted application of positive feedback from a physician, for example, is an effective strategy for enhancing treatment compliance. Exemplar techniques include modifying behavior with contingency contracts (e.g., formal written agreements between two individuals that outline the behaviors that are to be modified and the rewards that follow the performance of those behaviors).

Cognitive psychotherapy focuses on conscious thought processes. It is primarily based on two principles: first, cognitive processes are a primary determinant of behavior; and second, cognitive restructuring (i.e., modifying assumptions and beliefs) may produce behavioral and emotional change and alleviate illness. The cognitive model views psychiatric symptoms as being produced by inappropriate patterns of thought or cognitive distortions. For example, most depressed people automatically interpret situations in negative ways (refer to Table 43.4 for examples). If individuals recognize and change these illogical thought patterns, symptoms improve. Cognitive psychotherapy is indicated for depressed or anxious patients who demonstrate the ability for self-insight. Cognitive-behavioral therapy is time limited, generally occurring weekly, and it follows specific published protocols (54).

TABLE 43.4 COGNITIVE DISTORTIONS IN DEPRESSION

DISTORTION	DESCRIPTION
All-or-nothing thinking	Seeing things in black-and-white categories. If performance or situation is less than expected, then it is perceived as a total failure, unacceptable, etc.
Overgeneralization	Seeing a single negative event, no matter how minor, as part of a never-ending pattern of defeat.
Mental filter	Exclusively focusing on one negative to the exclusion of others so that your vision of reality becomes entirely centered on this one issue.
Disqualifying the positive	Rejecting positive experiences by insisting that they do

	not count for some reason or another. You can then maintain a consistent negative self-bias even though everyday experiences contradict your perception.

Jumping to conclusions
  a. Mind-reading
  b. Fortune-telling error
	Making a negative interpretation even though there are no definite facts that convincingly support the conclusion.
	
	Creating arbitrary conclusions that people, situations, and things are reacting to you negatively.
	
	Anticipating that situations will not turn out well, you feel convinced that your prediction is already an established fact.

Magnification	Exaggerating the importance or relevance of things (such as failure, incompletion, another person's achievements).
Catastrophizing	Amplifying the consequences of ambiguous or negative events or situations.
Minimization	Inappropriately reducing your (or someone else's) skills and strengths until they are negligible factors.
Emotional reasoning	Issuing greater importance to negative feelings than is realistic: "I feel bad, therefore it must be true."
Should statements	Statements about self and others that reflect expectations of behavior or situations ("I *should* be more competent; I *need* to be happy all the time"). Should statements directed at the self usually produce feelings of guilt. Similar statements directed at others often generate feelings of anger and resentment.
Labeling and mislabeling	An extreme form of overgeneralization. Rather than describing the situation, labels are assigned to the person or self ("I am a terrible person not worthy of love from another"). This often includes using colorful language expressing strong emotions.
Personalization	Viewing yourself as the origin or cause of a problem.

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Empiric research and clinical management of psychiatric conditions among allergy patients have dramatically advanced in the past decade. A variety of effective pharmacologic and psychotherapeutic interventions are available for treatment of the many psychiatric illnesses seen in individuals with atopic diseases. With more recent attention to clinical demands for responsiveness, the treatment of mental illness is beginning to close the gulf between research and clinical practice.

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In Vivo and *In Vitro* Testing in Allergy and Immunology

MELANIE M. MAKHIJA

Assessment of disease in allergy and immunology involves clinical testing, both *in vivo* and *in vitro,* in addition to clinical history and physical examination. Clinical history is of utmost importance in determining which type(s) of testing to pursue. This chapter reviews the commonly used *in vitro* and *in vivo* testing modalities in the fields of allergy and clinical immunology.

■ TESTS FOR ALLERGIC DISEASES

Skin-Prick Test

Epicutaneous skin-prick testing (SPT) is the preferred method of testing for detection of allergen-specific immunoglobulin E (sIgE) antibody. It is performed for food allergy, perennial and seasonal environmental allergies (aeroallergens), some medication allergies (i.e., penicillin), and for venom allergy. It is also used for latex allergy in Europe and Canada; however, commercial extracts of latex allergen are not available in the United States.

There are several practice parameters that have been published outlining SPT (1–3). SPT involves placing a drop of commercially available allergen extract solution (1:10 or 1:20 weight/volume) on the skin of the volar aspect of the lower arm or the back. The extract is introduced into the epidermis with a testing device, which may be a lancet or plastic SPT or multiprick testing device. A reaction is read 15 to 20 minutes after test placement. The testing detects sIgE bound to skin mast cells via a wheal-and-flare (redness) response. The wheal is measured using the largest diameter in millimeters or the longest diameter plus the orthogonal diameter divided by 2. Positive (histamine) and negative (saline) controls are applied together with the allergens to ensure validity and to control for issues that may cause false positives (such as dermatographism) or false negatives (premedication with antihistamines). A wheal diameter of ≥3 mm

larger than the negative control is considered positive, but package inserts of some reagents may have different criteria. The stability and concentrations of allergen extracts may limit the quality of skin testing. The size of a skin test may vary based on the person doing the test, the location of the test (back versus forearm), the device used for testing, and whether the testing is performed in the patient's allergy season if pollen allergic (2). SPT should not be performed for 1 month after an anaphylactic reaction, because the skin testing may be falsely nonreactive during this period.

SPT to foods has a low specificity and low positive predictive value. Positive skin testing indicates sensitization to an allergen only. Unless there is a corroborative clinical history, a definitive diagnosis of food allergy cannot be made based on skin testing alone (4). The sensitivity and negative predictive value of SPT is very high (>90%) for most food allergens with the exception of food with thermolabile molecules; therefore, negative testing is generally predictive of tolerance (5).

The advantages of SPT include that it is standardized and inexpensive compared to *in vitro* testing. In addition, results are available within 15 to 20 minutes. Skin testing is useful for evaluating reactions to unusual allergens because solutions for skin testing can be made from different allergens, including fresh foods, inhalants, and medications, even if a commercial extract is not available.

There is a risk of systemic reaction to SPT. This risk may be increased if using a noncommercial extract for testing. Patients with poorly controlled asthma, with poor spirometry or peak flow readings, may be at increased risk of systemic reaction, including anaphylaxis. Also, patients with significant cardiovascular disease and pregnancy may be at risk of more significant reactions to anaphylaxis, and treatment with epinephrine should be necessary.

Late reactions to SPT may occur, including redness and swelling at testing sites, anywhere from 1 to 2 hours after testing. They typically resolve in 24 to 48 hours. Late reactions are not useful for the diagnosis of IgE-mediated allergy.

Intradermal Skin Test

Intradermal testing is used for aeroallergen testing in adults and is also useful for drug and venom allergy. Intradermal testing is more sensitive and reproducible than SPT; however, there is an increased risk of systemic reaction. It should only be performed when SPT is negative. Intradermal skin testing involves using a 26- or 27-gauge needle, such as a tuberculin syringe, to administer allergen

intracutaneously. 0.02 to 0.05 mL of a 1:500 to 1:1,000 weight/volume of allergen is injected into the skin to form a small bleb, and the test is read 15 to 20 minutes later. A negative control is used to control for false positives. The response is measured by the size of the wheal at the site of injection. The wheal is measured using either longest diameter or the longest diameter plus the perpendicular diameter divided by 2 as with epicutaneous testing. The definition of a positive intradermal test as per the American Academy of Allergy, Asthma and Immunology is any wheal that is larger than the negative control; however, allergists also sometimes use a 3-mm wheal or a 5-mm wheal as cutoffs for positive tests (3). Evidence-based guidelines are lacking. Intradermal testing is not currently used for food allergy or latex allergy because of a high risk of systemic reactions.

Allergen-Specific IgE

Allergen-sIgE testing is the most common laboratory test used to diagnose Immediate or type I hypersensitivity reactions to foods or reactivity to aeroallergens. It can be used as an alternative to SPT in patients with contraindications to skin testing such as dermatographism or those who cannot be taken off antihistamines. It is also performed as an adjunct test to SPT for food allergy, because sIgE levels to foods can be trended and followed over time. The Phadebas radioallergosorbent test (RAST) (Pharmacia, Uppsala, Sweden) was the first assay used for the detection of the allergen-sIgE antibody. The methodology for this test involves binding an antigen (allergen) to a paper disk or other solid phase and then incubating it with human serum. A buffer wash removes unbound serum proteins, and radiolabeled antihuman IgE is added to detect bound IgE. The results are reported in units per mL of IgE (6). The term radioallergosorbent test (RAST) was originally a brand name, but it is still used incorrectly in practice to describe any assay for sIgE. The RAST test is no longer used in practice, because sIgE tests using enzyme-linked immunosorbent assay (ELISA) to measure sIgE have been developed. These are more sensitive and specific than earlier methods, they do not require radioactive reagents, and are also more quantitative, reproducible, and automated in comparison. Multiple assays exist, including several Food and Drug Administration (FDA)–labeled completely automated systems, although none has been adopted as the industry standard (6). A study of three different assays showed that results were not comparable among systems (7). Currently, many allergists and laboratories use the Phadia ImmunoCap system, but there are others such as the Microtest (Microtest Diagnostics, London, UK) (8). ImmunoCAP uses a cellulose sponge

to bind to all relevant allergens and utilizes fluorescent anti-IgE in a quantitative fluorescence enzyme immunoassay. Results are reported quantitatively (<0.10 to >100 kU/L) but may also be reported by classes (0 to VI), although the class system is rarely used in allergy practice. sIgE testing reflects allergen sensitization and not true allergy. A clinical history is required to make an allergy diagnosis. Studies suggest that the higher the sIgE to foods, the more likely a reaction will occur. Several studies have looked at the likelihood of reaction with sIgE cutoffs for common allergenic foods; however, the predictive values for each food differ and vary among studies (9–16).

Pitfalls of the *in vitro* sIgE testing include false positives in patients with a high total IgE level because of nonspecific binding of allergen, resulting in low-level sensitization to several or all allergens tested (3). sIgG may also bind in the assay, blocking the binding of sIgE, resulting in false negatives. In addition, there is homology between some pollens and some foods in patients with seasonal allergic rhinitis, which may cause falsely elevated food sIgE testing owing to cross-sensitization. The quantity of sIgE may not directly reflect the biologically relevant mast cell-fixed antibody and does not correlate with the severity of clinical reactions. For some foods, the mix of minor and major allergenic components in the reagents may result in variation in positive and negative predictive value.

Many laboratories offer IgE panel testing for foods and/or inhalants. These panels are an easy way to obtain testing to multiple allergens at the same time and are often used by primary care physicians if a concern for allergy arises. Because of the reasons listed earlier, there is a high likelihood that some false positives will occur if a panel of sIgEs is performed. Therefore, panel testing can lead to incorrect interpretation and misdiagnosis of food allergy, overly restrictive dietary avoidance as well as an economic burden on the health system (17).

Component-Resolved Diagnostics

The FDA has approved allergen component-resolved diagnostic (CRD) testing using the ImmunoCAP system (Phadia Immunology Reference Library PiRL, Phadia US Inc.). CRD involves microarray testing to assess antigenic epitopes on major allergens. Knowledge of allergen component sensitizations may help differentiate between severe/anaphylactic allergy and other allergic diseases such as oral allergy syndrome and may also be useful for assessing cross-sensitization to aeroallergens to help determine appropriate immunotherapy (18,19). This

testing is used for major food allergy protein components, as well as fruits, vegetables, and several environmental allergens (aeroallergens). The most commonly used component testing for food allergy is to peanut. Multiple allergic components have been identified in peanut. Ara h 1, 2, 3, 6, 8, and 9 are thought to be the most important markers of peanut sensitization. The peanut component test panel includes testing for Ara h 1, 2, 3, 8, and 9. Ara h 6 is not included in the panel because it cross-reacts with Ara h 2 and rarely occurs in the absence of sensitization to Ara h 2 (20,21). Ara h 1, 2, and 3 are seed storage proteins, which are associated with risk of a systemic allergic reaction, including anaphylaxis. Ara h 2 is associated with severe reactions and is the strongest predictor of clinical allergy (22). Ara h 8 is a pathogenesis-related-10 protein that cross-reacts with pollens, especially birch and birch-related pollens. Sensitization to Ara h 8 is associated with milder, localized symptoms (i.e., oral allergy syndrome) and a low risk of systemic reaction. Patients who are only sensitized to Ara h 8 may be considered for oral food challenge to peanut (23,24). Ara h 9 is a lipid transfer protein. Sensitization to Ara h 9 can result in severe systemic reactions after peanut exposure in some patients. People sensitized to Ara h 9 are often also sensitized to Ara h 1 to 3 (25). Ara h 9 is not specific to peanut because it cross-reacts with pitted fruit (e.g., peaches) (26).

The ImmunoCAP Solid-phase Allergen Chip (Phadia, Thermo Fischer Scientific, Uppsala, Sweden) and other microarray systems like Microtest have demonstrated acceptable accuracy as compared to ImmunoCAP and SPT (27,28).

Total Serum IgE

Total serum IgE is helpful in determining atopic presentations. Patients with allergic conditions, including atopic dermatitis, asthma, and allergic rhinitis, often have elevated total IgE. This test is useful in certain clinical scenarios, including diagnosing diseases such as allergic bronchopulmonary aspergillosis or allergic bronchopulmonary mycosis. It is also tested in patients in whom the use of the humanized monoclonal anti-IgE drug, omalizumab (Xolair, Genentech, Novartis) is being considered for the treatment of moderate-to-severe asthma. A very high IgE level (>2,000 IU/mL) in a patient with recurrent infections, may indicate hyper-IgE syndrome, a primary immunodeficiency, as discussed in section "Primary Immunodeficiency Testing." A few other immunodeficiencies (including Wiskott–Aldrich syndrome) and some malignancies may also present with a high total IgE level.

Total serum IgE can not only be measured using the Phadia ImmunoCAP technology but is also measured with other technologies using ELISA. Briefly, the ELISA procedure involves fixing antihuman IgE monoclonal antibody to a solid surface, such as a microtiter plate or plastic bead, and then incubating it with human serum. IgE from the human serum binds to the antihuman IgE fixed on the plate, unbound serum components are washed away, and a secondary enzyme-conjugated (often horseradish peroxidase or alkaline phosphatase) antihuman IgE antibody is added. The excess conjugate is washed out, an enzymatic substrate is added, and the colorimetric change produced by the enzymatic reaction is detected spectrophotometrically. Results are quantitated by extrapolation from a standard curve of known IgE concentration included in the same microtiter plate (6). Results for total IgE are usually reported in IU/mL, kU/L, or ng/mL (1 IU/mL = 1 kU/L = 2.4 ng/mL of IgE).

Pitfalls of total IgE measurement include that it does not help determine which atopic condition a patient has and does not indicate which allergens a patient is sensitized to. There is a large range of total IgE levels in the population, including in nonatopic individuals, and concentration may be age dependent. Therefore, the overall clinical utility of a total IgE measurement is limited.

Patch Tests

The patch test was first described in the late 1800s as a test for type IV hypersensitivity reactions for contact dermatitis. It is the gold standard test for contact allergen sensitization. Patch testing for allergic contact dermatitis is discussed in Chapter 30.

The atopy patch test (APT) involves prolonged contact of an allergen to the skin, with the goal of mimicking a similar immune response to atopic dermatitis. Biopsy specimens of patch test sites show an initial T_H2 infiltration followed by a predominance of T_H1 cytokines and cells similar to atopic dermatitis (29,30). The reagents are applied to the patient's back in aluminum discs, such as Finn Chambers on Scanpore tape (Alerter Laboratories Inc., Petaluma, CA, USA), and are removed at 48 hours with a final read at 72 hours after application.

APT has been studied as a method to help identify food and aeroallergen triggers for atopic dermatitis. Although combined testing, including APT, in addition to SPT and sIgEs improves sensitivity and specificity of testing, it does not eliminate the need for oral food challenges and, therefore, is not recommended as part of the workup for atopic dermatitis at this time (31,32).

APT may have some utility in diagnostic testing for eosinophilic gastrointestinal disorders especially pediatric eosinophilic esophagitis (33,34) and possibly to assist in guiding the safe reintroduction of foods in children with food protein-induced enterocolitis syndrome (35).

Basophil Activation Test

The basophil activation test (BAT) is a flow cytometry-based assay that looks at the expression of activation markers on the basophils surface after incubation of the patient's blood with allergen. It may be considered in cases where skin testing or sIgE testing is not available. It has been validated in IgE-mediated conditions, including drug allergy, venom hypersensitivity, food allergy, and allergic rhinitis (36). In food allergy, the BAT has been shown to correlate with oral food challenge severity scores. This indication could help identify that patients are risk for severe reactions to oral food challenges (37). BAT is not currently used regularly in clinical practice.

Complementary and Alternative Testing

Complementary and alternative testing and treatment includes tests and treatments that are not scientifically proven to be effective in allergy diagnosis. These tests are listed in Table 44.1 and are further described in Chapter 45. They are not recommended or useful in diagnosis or treatment of atopic conditions.

TABLE 44.1 NONSTANDARDIZED TESTS USING COMPLEMENTARY AND ALTERNATIVE MEDICINE TECHNIQUES THAT ARE UNPROVEN FOR THE DIAGNOSIS OR TREATMENT OF ALLERGIC CONDITIONS

UNCONVENTIONAL DIAGNOSTIC METHODS IN ALLERGY

Applied kinesiology (muscle testing)

Hair analysis

IgG/IgG$_4$ testing for foods

Pulse testing

Electrodermal testing
Cytotoxic testing
Provocation–neutralization
Food immune complex assay
Unconventional Treatment Methods in Allergy
Homeopathic remedies
Neutralization
Injection of food extracts or urine
Detoxification
IgG, immunoglobulin G.

Precipitating IgG Antibodies

Precipitating IgG antibodies (precipitins) are used to test patients who have hypersensitivity pneumonitis induced by chronic exposure to organic dust antigens, such as molds (thermophilic actinomyces, *Aspergillus* species, etc.), grain dust, and feces/droppings from birds. However, this is not a perfect test because bird breeders and farmers have high levels of positive serum precipitants caused by prolonged exposure to inciting antigens. False negatives also occur with this test. Precipitating IgG testing is only available in specialized laboratories.

Serum Tryptase and Other Tests for Anaphylaxis

Mast cells have preformed mediators, including tryptase, which are used by allergists and emergency department physicians to measure systemic mast cell activation. Concentrations of α-tryptase correlate with mast cell number, whereas β-tryptase concentrations are associated with current (acute) mast cell activation.

Total serum tryptase can be used to confirm a diagnosis of anaphylaxis, although samples need to be collected within 4 hours of a suspected anaphylactic reaction. *β*-Tryptase levels are thought to peak 30 to 60 minutes after a reaction, with a half-life of 2 hours. Normal total tryptase ranges from 1 to 10 ng/mL. If baseline tryptase is >20 ng/mL in a patient without acute symptoms of anaphylaxis, indolent systemic mastocytosis should be suspected and further evaluation sought. Histamine elevation is short-lived after an anaphylactic episode; however, metabolites, such as *N*-methyl histamine and prostaglandins, can be measured in the urine for 24 hours after an anaphylactic event and may be useful for diagnosis. Other potentially useful biomarkers are being studied, including platelet-activating factor, bradykinin, chymase, and others (38).

Nasal Provocation

Nasal provocation is primarily a research test in North America; however, in some countries this test is used clinically. Nasal reactivity is thought to be predictive of bronchial reactivity to allergens (39). This test may be useful if the history of allergic rhinitis is highly convincing, but SPT, intradermal, and sIgE tests are negative. This test is also useful for the evaluation of occupational allergens or to demonstrate nonallergic irritant rhinitis. Nasal provocation is performed using dilute allergen extracts. The nose is examined for structural pathology, including polyps, septal deviation, or acute infection. A diluent solution (negative control) is then sprayed into one or both nostrils using a metered-dose delivery device to assess for nonspecific responses. Sneezes are counted over the next 15 minutes, and nasal discharge is collected. Pruritus, rhinorrhea, nasal stuffiness, and ocular symptoms are scored using a severity scale. If there are no symptoms, the provocation is performed every 15 minutes with increasing concentrations of serially diluted allergen. The downsides of nasal provocation include the multiple different techniques used for this test as well as the absence of standardized methods and reagents. Standardization may increase the utility of nasal provocation test for clinical practice (40).

TESTS FOR PRIMARY IMMUNODEFICIENCY DISEASES

Patients with primary immunodeficiencies present with recurrent or severe infections, autoimmunity, or both. In infants and young children, failure to thrive is a common presenting sign. Appropriate diagnostic testing is essential for early diagnosis. Immunologic testing is guided by the clinical presentation of the patient, including age, sex, type of infections, autoimmunity, and family history.

General testing includes a complete blood count (CBC) and differential to assess for abnormalities, including lymphopenia or neutropenia. Chemistry studies, including electrolytes, blood urea nitrogen and creatinine, glucose, and a urinalysis, may be helpful to exclude systemic disease causing a secondary immune deficiency. A low albumin suggests protein loss or malnutrition. Erythrocyte sedimentation rate or C-reactive protein may be elevated in infections and inflammatory disorders. Additional laboratory tests have been developed to assess the major components of the humoral and cellular arms of the immune system (41,42). A practice parameter outlining the approach to primary immunodeficiency, including diagnostic testing, was published in 2015 (43,44).

Humoral Immunodeficiency Testing

Patients who present with recurrent bacterial infections of the sinopulmonary tract should be tested for humoral immunodeficiencies. This includes measuring quantitative serum immunoglobulins (IgG, IgA, IgM, and IgE) and comparing them to age-matched normal ranges to detect a deficiency or excess in any of these. Most clinical laboratories use nephelometry to measure immunoglobulin levels quantitatively. Nephelometry measures scatter of light from a light source projected through the liquid sample in a transparent container. The scatter of light is proportional to the concentration of the immunoglobulin in the solution (6). As a general rule, a total serum IgG concentration of <400 mg/dL in adolescents or adults with recurrent infections, or values below the age-matched reference in children with recurrent infections warrant further workup for humoral immunodeficiency. Measurement of IgE is helpful to identify allergic disease in patients with recurrent sinus infections. A very high IgE level may indicate hyper-IgE syndrome in a patient with recurrent bacterial infections and dermatitis.

Further evaluation of humoral immunodeficiencies includes assessment of antibody function by measuring specific antibody responses to previous immunizations that the patient has received. A patient with low levels of antibody to a vaccine can be immunized with protein (i.e., tetanus toxoid, diphtheria, pneumococcal conjugate, *Haemophilus* influenza type B) or polysaccharide antigen (i.e., pneumococcal polysaccharide). Repeat antibodies should be measured 4 to 6 weeks after vaccination to confirm the patient's ability to make specific antibodies. Polysaccharide response is not useful in children <24 months of age. Addition testing of humoral immunity includes measurement of is hemagglutinins, which are polysaccharide IgM antibodies that

cross-react with A and B blood group antigens. Isohemagglutinins develop during the first year of life; therefore, they will be low in patients <1 year of age and in those individuals how have AB blood group.

Cellular and Combined Immunodeficiency Testing

Cellular immunodeficiencies are caused by defects affecting T cells. T-cell deficiencies are also considered combined deficiencies because antibody production by B cells requires functioning cellular immunity. Cellular and combined deficiencies are the most severe immunodeficiencies. These diseases present with severe viral and bacterial infections, as well as opportunistic infections.

T-cell defects are evaluated initially with a white blood cell count and differential. Marked lymphopenia (<2,500 cells/µL) in an infant, or <1,500 cells/ µL in a patient over 5 years of age, warrants further evaluation. HIV infection should be ruled out by polymerase chain reaction/viral load. Further testing involves lymphocyte immunophenotyping. Flow cytometry is used to measure the relative percentages and absolute numbers of the major lymphocyte subsets via surface markers (in parentheses), that is, B cells (CD19), absolute T cells (CD3), natural killer (NK) cells (CD16/56), T-helper cells (CD4), and cytotoxic T cells (CD8). Naïve and memory T-cell percentages may also be helpful in determining whether an infant has only maternal T cells. Lymphocyte subset numbers and relative percentages can be compared with age-matched reference ranges. Note that lymphocyte subset numbers may be significantly decreased in the setting of illness, including infection, and due to immune suppression. A CBC with differential should be obtained at the same time as the sample sent for flow cytometry analysis to determine a total lymphocyte count.

Flow cytometry uses lasers which are focused on a fluid stream containing cells, because they pass single file through the flow cytometer. The cytometer captures the scattered laser light in both a forward (roughly correlating to size) and at a right angle (roughly correlated with the internal complexity of the cell) as well as light emitted by the fluorochromes which are conjugated to antibody (usually monoclonal antibody, mAb). The mAb are directed against specific targets (e.g., CD4) on specific cells (e.g., CD3$^+$ T cells). Based on their innate physical properties, lymphocytes generate specific light scatter signals, which allow them to be differentiated from monocytes and granulocytes. The lymphocytes will also emit a specific fluorescence signal(s) depending on the specific mAb bound to their surface. Various panels of mAb are designed to

measure very specific subsets of lymphocytes based primarily on the expression of different clusters of differentiation (CD) (6). Abnormalities in the relative representation of lymphocyte subsets are readily identified and known to be associated with specific primary immunodeficiency diseases. It is also possible to measure the expression of known antigens associated with specific primary immunodeficiency diseases (e.g., CD40 ligand, MHC class I, interleukin-2Rγ chain, CD3 chains); however, because of the rare incidence of many of the primary immunodeficiency diseases and the relative complex and expensive nature of these more specific flow cytometry-based tests, they are only performed in highly specialized laboratories.

T-cell function can be assessed by stimulating T cells nonspecifically with mitogens (e.g., phytohemagglutinin, concavalin A, pokeweed mitogen) or with monoclonal antibodies (anti-CD3) and comparing them with age-matched controls (43,44). Low proliferation to nonspecific stimuli indicates poor T-cell function. Mitogen stimulation can be assessed at any age. The results are interpreted as normal if <50% of control. Additionally, lymphoproliferation to specific antigens (candida, tetanus, and tuberculin) can be assessed in the same manner but should only be used in patients >24 months of age. If 22q11 deletion syndrome (DiGeorge syndrome) is suspected, chromosomal studies, including multiple ligation-dependent probe amplification or fluorescence in situ hybridization for the microdeletion, can be performed.

Measuring the number of T-cell receptor excision circles (TRECs) in dried blood spots has recently been adopted by many states in the United States and several other countries as a newborn screen for severe combined immunodeficiency (SCID). TRECs are circular pieces of DNA formed as T cells rearrange their TCR genes during T-cell maturation in the thymus. TRECs do not replicate; therefore, the number of TRECs correlates with the production of new T cells from the thymus. TRECs numbers have also been measured for evaluating the severity of T-cell depletion in patients with 22q11 deletion syndrome and for evaluating immune reconstitution after bone marrow transplantation although this last indication has not been widely adopted. TRECs are measured using appropriate DNA primers and quantitative DNA amplification techniques.

Assessment of the breadth of the T-cell repertoire can also be performed for patients with primary immunodeficiency diseases, including Omenn syndrome, who develop only a few mature T-cell clones in the periphery. This is called oligoclonal expansion. A relatively easy method to measure the T-cell repertoire

can be performed using a panel of monoclonal antibodies directed against 24 Vβ family-specific targets on the T-cell receptor. Each of the 24 TCR Vβ chain families is found in healthy subjects. In patients with Omenn syndrome, atypical DiGeorge syndrome, or leaky SCID only a few Vβ families will be represented.

Complement Deficiency Testing

Complement deficiency screening is performed in patients with recurrent sinopulmonary infections (C2 deficiency), pyogenic infections (C3, factor I, and factor H), systemic lupus erythematosus–like symptoms of autoimmunity (C1q/r/s, C2, and C4 deficiencies), or susceptibility to *Neisserial* infections (terminal complement defects C5 to C9, factor D, or properdin deficiencies). Testing involves complement function screening of both the classic (CH50) and alternative (AH50) pathways and assessing specific complement component levels when the function is markedly decreased. A decreased AH50 test suggests problems with factor B, factor D, or properdin. Decreased CH50 and AH50 suggest a defect in a shared complement component (C3 to C9).

Tests for Phagocytic Defects

Screening for phagocytic (neutrophil) defects is performed in patients who have recurrent fungal and bacterial infections. Initial screening includes a CBC and differential, looking for leukocytosis or severe neutropenia. Neutrophil function is assessed by testing for specific diseases. Chronic granulomatous disease testing is performed using a flow cytometry assay and an oxygen-sensitive dye, dihydrorhodamine 123, to measure the ability of granulocytes to exhibit an oxidative burst *in vitro* or can be done using the older nitroblue tetrazolium test. Leukocyte adhesion deficiency testing is also performed by flow cytometry, assessing adhesion molecules on neutrophils (CD11 and CD18 or CD15), which are absent or decreased in this disorder. An elevated IgE level may indicate hyper-IgE syndrome. A peripheral blood smear may be useful to identify giant azurophilic granules in neutrophils, eosinophils, and other granulocytes, which are diagnostic of Chediak–Higashi syndrome.

Other Immunodeficiency Testing

Testing for other immunodeficiencies is varied and is disease specific. A few examples include autoimmune lymphoproliferative syndrome (ALPS) (increased number of CD3$^+$ cells that are negative for CD4 and CD8 [double negative], expressing the α/β form of the T-cell receptor); IPEX (diminished or absent FOXP3 protein in the nucleus of CD4 T cells); ataxia telangiectasia (α-

fetoprotein measurement and radiosensitivity testing); autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)/chronic mucocutaneous candidiasis (autoimmune regulator [AIRE] or other genetic sequencing), hyper-IgE syndrome (highly elevated total IgE level and genetic sequencing abnormality in the STAT3, DOCK8, TYK2, or SPINK5 genes) or X-linked lymphoproliferative disorder presenting with hemophagocytic lymphohistiocytosis (NK-cell testing and genetic sequencing), and toll-like receptor pathway testing for disorders, such as IRAK4, MYD88, and NEMO.

Next-Generation Sequencing

Next-generation sequencing techniques, including whole genome and whole exome sequencing, are now being used to help identify novel genetic mutations in patients with immunodeficiencies in which the genetic basis is unknown (45,46). A recent observational study of exome-sequenced patients with suspected genetic disorders reported a molecular diagnosis rate of approximately 25% (47). In this approach, sequenced exomes are aligned with reference genomes, allowing identification of disease-related mutations. Candidate variations are then screened through databases that provide information on allele frequency, allowing elimination of mutations that do not match disease occurrence or the predicted method of inheritance.

For both allergic diseases and primary immunodeficiency disorders, laboratory-based testing for immunodeficiencies is imperative in guiding correct diagnosis and management; however, testing should be used judiciously in patients in whom a high level of suspicion is present.

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Controversial and Unproved Methods in Allergy Diagnosis and Treatment

ABBA I. TERR

Unconventional and unproved procedures, theories, and practices are often referred to as "complementary and alternative medicine" (1) or "integrative medicine" (2). Patients with allergy are often subjected to these practices (3–8). However, there is no evidence that they alternate, complement, or participate in rational scientifically based medical practice. Furthermore, the risks of undertreatment and side effects have not been adequately addressed (9).

Accurate diagnosis and effective therapy of allergic disorders can be achieved by practices that rely on sound theory and scientific clinical research referred to as "evidence-based medicine" that is efficient, safe, and cost-effective. There is no justification today for an empirical approach to allergy.

DEFINITIONS

Standard practice employs methods of diagnosis and treatment used by reputable physicians in a particular subspecialty or primary care practice. It usually involves a range of options tailored to the individual patient's clinical status. Physicians knowledgeable, trained, and experienced in allergy may prefer certain accepted diagnostic and therapeutic methods while also recognizing that other methods are equally appropriate. Acceptable methods are consistent with established mechanisms of allergy and evaluated by properly conducted scientifically based clinical trials that demonstrate efficacy and safety.

Practice guidelines or *parameters* are frequently published by specialty societies, governmental agencies, or health insurance carriers based on opinions of experts. Evidence-based guidelines are defined as "systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances" (10), thereby promoting both clinically effective standards and cost-effective care. Occasionally, these are generated by formalized, iterative questionnaires, such as the Delphi method

(11).

Experimental procedures are potentially new methods of practice resulting from scientific studies or chance empiric observation. Experimental methods of diagnosis and treatment are those currently undergoing clinical trials on subjects fully cognizant of the experimental nature of the procedure, their potential benefits and risks, and with their informed consent to participate in experimental trials.

Controversial or *unproved methods* refer to those procedures that lack scientific credibility and proven clinical efficacy, even though they may be used some physicians in their practices. Most of the controversial methods discussed in this chapter have been tested in clinical trials that reveal either ineffectiveness or insufficient data to establish effectiveness. In some cases, anecdotal testimonies are the only available "evidence."

Alternative and *complementary*, as stated earlier, are not appropriate terms, because they tend to obscure the essential issue of validation for clinical use by proper scientific scrutiny. Many physicians who use controversial allergy practices, however, do so because they sincerely believe them to be worthwhile despite evidence to the contrary. The clinician who treats allergic patients should be sufficiently knowledgeable about both accepted and unproved theories and techniques in order to counsel their patients who inquire about controversial methods.

Fraud and *quackery* generally refer to medical practices performed by those individuals who knowingly, deliberately, and deceitfully use unproven and controversial methods for profit.

Standard of care is the terminology usually used in the course of litigation. The definition will vary according to jurisdiction.

CONTROVERSIAL ALLERGY THEORIES

Unproven and controversial theories about allergy are the basis for unconventional diagnostic and treatment practices.

Clinical Ecology

The practice known as clinical ecology (12–15), originally postulated that allergic disease stems from a failure of humans to adapt to synthetic chemicals (16). It is based on theories that common environmental substances are toxic to the human immune system (17) or that normal homeostasis is exhausted by

ingestion of foods and inhalation of chemicals. Certain concepts, such as a maximum total body load of antigen, masked food hypersensitivity, and a "spreading phenomenon" whereby the presence of one specific allergy induces others of different specificities, are both unique and unscientific.

Clinical ecology practitioners believe that systemic complaints of fatigue, lethargy, weakness, body aching, nervousness, irritability, mental confusion, sluggishness, and poor memory—in the absence of any clinical sign of allergic inflammation—are caused by exposure to environmental allergens. The "allergens" most often implicated are low-level environmental chemicals, foods, food additives, and drugs (18,19). Specific chemicals, such as those used in carbonless copy paper (20), dental amalgams (21), or even electromagnetic fields (22), have been implicated.

"Diagnoses" include ecologic or environmental hypersensitivity disease, chemical hypersensitivity syndrome, chemical AIDS, 20th-century disease, total allergy syndrome, cerebral allergy, and allergic tension fatigue syndrome. Publications on this subject are largely anecdotal. No definitive controlled studies have yet shown the existence of such a syndrome (23). Patients often claim dramatic improvement from eliminating certain foods and/or avoiding chemical exposures, but this is not supported by scientific evidence, and the improvement is often transient. Currently, the number of practitioners who subscribe to the clinical ecology theory is unknown.

Allergic Toxemia

The allergic toxemia concept encompassed by clinical ecology asserts that allergy causes certain psychiatric conditions from a presumed toxic effect on the brain. Attention deficit hyperactivity disorder in children has been attributed to food coloring, preservatives, and other additives (24). Properly controlled studies, however, do not support this concept (25,26). The claim that ingestion of wheat and certain other foods cause or contribute to adult schizophrenia (27,28) is also unconfirmed.

Idiopathic Environmental Intolerances (Multiple Chemical Sensitivities)

The illnesses diagnosed by clinical ecologists were encompassed for many years by the term "multiple chemical sensitivities." Idiopathic environmental intolerances (IEI) is a more appropriate name, because it does not imply (unproved) mechanisms (29). Patients with these diagnoses almost always have

multiple wide-ranging subjective complaints without specific physical findings or diagnostic laboratory test results (30–32). Although clinical ecologists have postulated a purely untested theory of "neural sensitization" (33), many other studies indicate that IEI complaints are compatible with conversion reactions, anxiety and depression, psychosomatic illness (21,34–36), or interpreted as a belief system (34) or a conditioned response (37).

Gulf War Syndrome

Some personnel serving in the 1991 Persian Gulf War have reported illness identical or similar to IEI, often implicating battlefield chemicals as the cause (38,39). This may be reminiscent of "shell shock" of World War I or other previous conflicts. The published studies are contradictory regarding physical and psychologic etiology (40).

Candida Hypersensitivity Syndrome

Candida albicans is a nonpathogenic component of the microflora of the gastrointestinal and female genitourinary mucous membranes in a substantial portion of the population without illness (41). Certain physiologic and pathologic conditions—such as pregnancy, diabetes mellitus, endocrine diseases, a defective local or systemic immunity, or medications—result in opportunistic infection and clinically significant candidiasis. Persons with no such predisposing factors are said to suffer an illness known as Candida hypersensitivity syndrome (42,43). Clinically, the syndrome is indistinguishable from environmental illness. *C. albicans* has also been claimed to cause behavioral and emotional diseases and a variety of physical illnesses and subjective symptoms. The diagnosis is made by history without confirmative testing. This syndrome is reminiscent of the concept of autointoxication that was popular in the early 20th century. In the opinion of some practitioners of that era, the bacterial component of the normal intestinal flora was considered to cause numerous physical and psychologic disabilities (44). A systematic review of intestinal Candida colonization failed to substantiate the existence of the "Candida hypersensitivity syndrome" (41).

Toxic Disease from Indoor Molds

Atmospheric mold toxicity has recently replaced environmental chemical sensitivity as a presumed cause of a variety of subjective complaints or illnesses in persons living in homes or working in buildings that have sustained water damage from flooding or excessive humidity, promoting indoor mold growth

(45). Fungi are a major component of the environment, and fungal spores are almost always present in the atmosphere. In contrast to well-recognized infectious and allergic diseases caused by molds, a combined toxicity/hypersensitivity theory is often invoked (46,47) as it is in the case of environmental illness.

One particular fungus, *Stachybotrys atra (chartarum),* has created considerable publicity because of the suspicion that *Stachybotrys* mycotoxin was the causative agent in cases of pulmonary hemorrhage/hemosiderosis in young infants living in water-damaged homes (48). The role of the mycotoxin in these cases has been called into question (49), but there remains unsubstantiated fear of the presence of any indoor mold spores as pathogenic. This unproved theory should not be confused with allergic diseases caused by fungal allergy, especially asthma, some cases of hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis (ABPA), and allergic fungal sinusitis. These can be identified by localized symptomatology, objective physical findings, functional and imaging studies that confirm pathology, and the presence of the relevant immune response by the patient.

Other Unconventional Practices

Acupuncture, Chinese herbal therapy, homeopathy, naturopathy, and similar "alternative" practices have all been used for allergy "treatment." None of these are based on accepted scientific principles of physiology, immunology, or pharmacology. Scientifically rigid clinical trials are difficult to achieve, but reasonably acceptable ones have failed to show benefit as allergy therapy (50–52).

UNCONVENTIONAL DIAGNOSTIC METHODS

Inappropriate tests to diagnose allergy or specific allergens can be categorized as: (1) procedures of no possible diagnostic value under any circumstances, (2) procedures that are intrinsically capable of a valid measurement but not appropriate for allergic disorders, and (3) procedures that are intrinsically capable of being used in allergy diagnosis but not for general clinical use because of low sensitivity or specificity, lack of general availability, or expense; for example, the *in vitro* histamine release test has been invaluable for allergy research, but it cannot be currently recommended for clinical use.

A thorough history and physical examination are considered to be essential for diagnosis by experienced allergists. Laboratory testing is used selectively to

supplement these clinical findings, especially when objective measurement of a functional abnormality such as airway obstruction is indicated, or when alternative diagnoses must be considered. *In vivo* allergy tests, such as skin-prick or intradermal tests, patch tests, or *in vitro* serum antibody tests, are procedures that detect the presence of an immune response of a particular type (e.g., immunoglobulin E [IgE] antibody or cell-mediated immunity) to a specific allergen. These tests alone do not diagnose or necessarily predict a clinical allergic disease. They do, however, assist the clinician in diagnosis when the results are correlated with the patient's history and physical examination.

"Diagnostic" Procedures of No Value Under Any Circumstances

The procedures included in this category are not based on sound scientific principles, and they have not been shown by proper controlled clinical trials to be capable of assisting in the diagnosis of any condition (53).

The Cytotoxic Test

This is also known as the leukocytotoxic test or Bryan test (54,55). It is promoted as a test for allergy to both foods and drugs. The procedure consists of the microscopic examination of an unstained wet mount of whole blood or buffy coat on a slide that had been previously coated with a food extract. Subjective impressions by microscopy of leukocyte swelling, vacuolation, crenation, or other changes in morphology are designated as a "positive" test result, that is, as evidence of allergy to the food. This "test" has not been standardized for time of incubation, pH, osmolarity, temperature, or other conditions that may be responsible for the observed changes (55). Test reproducibility has not been established.

There are no allergic diseases currently recognized as being caused by leukocyte cytotoxicity from foods, either immunologically or toxicologically. Some drugs do occasionally cause immunologically mediated cytotoxicity (e.g., immune granulocytopenia from cephalothin), but the Bryan test is not capable of diagnosing this condition. Controlled clinical trials fail to show that food allergy can be detected by this test (56).

Antigen Leukocyte Cellular Antibody Test

A modification of the cytotoxic test, the antigen leukocyte cellular antibody test (57), uses electronic instrumentation and computerized data analysis to examine and monitor changes in cell volumes. Like the cytotoxic test, it has also been

promoted as a screening procedure for diagnosing food allergy or intolerance. It has also been recommended for testing a host of other conditions, including arthritis, urticaria, bronchitis, gastroenteritis, childhood hyperactivity, rhinitis, and atopic dermatitis, for which the results are used to recommend elimination diet treatment for these diseases. There are no proper controlled trials to establish diagnostic efficacy (58,59).

Provocation–Neutralization

This is a procedure claimed by its proponents to diagnose "allergy" to foods, inhalant allergens, environmental chemicals, hormones, and microorganisms, such as *C. albicans*. The patient is given a small dose of an extract of one of these substances by either intracutaneous injection, subcutaneous injection, or by sublingual drop. Any subjective "sensations" (i.e., symptoms) during the following 10 minutes are recorded as a positive test result and thereby diagnosed as "allergy" to that substance. If the test is negative (i.e., no recorded sensations), it is repeated at higher concentrations until the patient reports a sensation. Progressively lower concentrations are then administered, and if fewer or no symptoms are reported, the reaction is reported as being "neutralized" (60–66). The neutralizing dose is then utilized as ongoing therapy.

The test result is graded as positive regardless of whether or not the reported sensations are the same as those in the patient's initial history. When the test is performed by intradermal injection, increasing wheal diameter with increasing dose is considered corroborative evidence of a positive test result. Some proponents measure change in pulse rate during the test, but there is disagreement about its significance.

Published reports of provocation–neutralization testing yield conflicting results (5,23). Studies have included subjects with varying clinical manifestations, different testing methods, and variable criteria for a positive test result. Many lack relevant controls, reflecting the absence of standardization and the subjective nature of provocation–neutralization.

Based on current knowledge of immunologic disease, there is no rationale for the provocation of subjective symptoms and their immediate neutralization under the conditions used in this procedure (30). A placebo-controlled double-blind evaluation of provocation–neutralization for diagnosis of food allergy in 18 patients concluded that symptoms were provoked with equal frequency by food extracts and by placebo (67), showing that results are based on suggestion (68). Furthermore, there is a potential danger of an adverse allergic reaction (69) in testing with an allergen to which the patient has significant IgE sensitivity. The

procedure is time consuming, because only a single concentration of one allergen can be "tested" at one time.

Electrodermal Diagnosis (Electroacupuncture and Bioresonance)

This procedure purports to measure changes in skin resistance after the patient is exposed to an allergen (70). The allergen extract, usually a food, is placed in a glass vial on a metal plate in an electrical circuit between two electrodes on the skin. A galvanometer is used to detect a decrease in skin electrical resistance compared to an empty vial. This is said to indicate allergy to the food.

There is no rational basis for such a "test" and no publications to support its use. Proponents use acupuncture points on the skin when performing this unconventional procedure, often referred to as electroacupuncture or bioresonance. Controlled studies demonstrate that it was incapable of detecting specific allergic sensitivities (71–73).

Applied Kinesiology

In applied kinesiology, the muscle strength of a limb is measured before and after the patient is exposed to a test allergen (74). Exposure to the allergen, usually a food, is done by placing a glass vial of the allergen in the patient's hand (or elsewhere on the skin), and muscle strength of the arm is estimated subjectively. A loss or weakening is considered a positive test result, indicating allergy to the tested food.

There is no scientific rationale behind the concept that allergy to a food or to any other allergen changes the function of skeletal muscle, and the belief that any exposure to the allergen could occur through a glass vial on contact with the skin is clearly untenable.

Diagnostic Procedures Misused for Allergy "Diagnosis"

The procedures included in this category are ineffective for allergy diagnosis, although they may be useful in the diagnosis of other medical conditions. They are considered under two categories: nonimmunologic tests and immunologic tests.

Nonimmunologic Tests That Are Inappropriate for Allergy Diagnosis

Certain procedures are valid diagnostic tests for certain conditions, although not when used for allergy. Those discussed here are the pulse test and quantitation of chemicals in body fluids and tissues. These tests have been promoted for allergy diagnosis based on erroneous concepts of the pathogenesis of allergy.

Pulse Test

Measuring a change in pulse rate—either an increase or a decrease after a test substance is ingested or injected—has been used by some as indication of allergy (75). A change in pulse rate occurs from a variety of physiologic conditions and during the course of many other diseases. There is no rationale or documentation that an increase or decrease in heart rate by itself can diagnose allergy.

Testing for Environmental Chemicals in the Body

Some physicians subscribe to the unsubstantiated belief that all synthetic chemicals, irrespective of dose, are toxic to the human immune system, resulting in "sensitivities" to numerous chemicals, foods, drugs, and other agents (76,77). Samples of whole blood, erythrocytes, serum, urine, fat, and hair are analyzed for the presence of environmental chemicals. The chemicals tested are typically organic solvents, other hydrocarbons, and pesticides. Analytical methods and instrumentation are available for quantifying almost any chemical at the level of parts per billion, and indeed many environmental chemicals are found at this low level in almost everyone because of the ubiquitous presence of these substances in today's environment. Under some circumstances, it may be appropriate to detect toxic quantities of a suspected chemical where poisoning is suspected, but the presence of such chemicals in the body, regardless of quantity, bears no relationship to allergic disease. The concept of an immunotoxic cause of allergic "sensitivity" is unproved.

Immunologic Tests Inappropriate in Allergy Diagnosis

The immunologic pathogenesis of allergic diseases of types I, II, III, and IV have long been firmly established firmly established. These involve IgE antibodies, immune cytolysis, immune complexes, and cell-mediated hypersensitivity, respectively. Other nonallergic diseases with immune mechanisms involve these and other pathways. Clinical laboratories offer sensitive and specific tests for detecting immunoglobulins, complement components, circulating immune complexes, blood levels of lymphocyte subsets, mediators of allergic inflammation, and other measurements of immune function. However, their use in allergy diagnosis may not be appropriate for this purpose, based on unproven theories discussed earlier. Examples of those that are promoted but inappropriate are given below.

Serum Immunoglobulin G Antibodies

Detecting serum IgG antibody to the relevant antigen may be diagnostic for those immune complex diseases where the immunogenic antigen is known or

suspected, that is, serum sickness or ABPA.

Detection of IgG and/or IgG$_4$ antibodies to food allergens has been promoted as a test for food allergy (53,78). Circulating IgG antibodies and postprandial immune complexes to foods are probably normal phenomena and not indicative of disease (79). IgG antibodies to foods or inhalant allergens are not involved in the pathogenesis of atopic diseases, although an IgG$_4$ response to immunotherapy is often observed and may represent "blocking antibodies." The "food allergy profile" (IgE and IgG measurements of food antibodies) is therefore diagnostically illogical (78). Although some allergists have speculated that adverse delayed reactions to foods may be caused by circulating immune complexes containing IgG or IgE antibodies to foods (80–82), this concept is unproved. Therefore, measurement of serum IgG antibodies or immune complexes has no diagnostic value in the management of atopic patients.

Total Serum Immunoglobulin Concentrations

Quantifying the total serum concentrations of IgG, IgA, IgM, and IgE can be accomplished easily and accurately. Significant reductions of one or more of these define the immunoglobulin deficiency diseases (83). Polyclonal increases in the serum concentrations of these immunoglobulins occur in from certain chronic infections and autoimmune diseases, and monoclonal hyperproduction occurs in multiple myeloma and Waldenstrom macroglobulinemia. Alterations in the total serum concentration of IgG, IgA, and/or IgM are not found in allergic disorders so that these measurements are not indicated.

Total serum IgE concentrations are generally higher in atopic than in nonatopic individuals. It is higher in allergic asthma than in nonallergic rhinitis and very high in some patients with atopic dermatitis. However, the total serum IgE is not a useful diagnostic "screen" for the patient with suspected atopic disease, because a significant number of atopic patients have concentrations that fall within the range of those who are nonatopic. Furthermore, it offers no information about antibody specificity necessary for allergy diagnosis. In ABPA, the total serum IgE concentration may have prognostic significance because it correlates with disease activity (84).

Lymphocyte Subset Enumeration

Lymphocyte subsets are identified by specific cell surface markers, termed clusters of differentiation. Quantifying lymphocyte subsets in blood is useful in the diagnosis of lymphocyte cellular immunodeficiencies and lymphocytic leukemias, but not in allergy. The "normal" range of circulating levels for many

of these subsets is wide and fluctuates under physiologic conditions.

Food Immune Complex Assay

Some commercial clinical laboratories offer tests that detect circulating immune complexes containing specific food antigens purportedly for the diagnosis of food allergy. The method involves a two-site recognition system in which a heterologous antibody to the food is bound to a solid-phase immunosorbent medium (85,86). When incubated with the test serum, the reagent antibody detects the antigen within the immune complex, which is then detected and quantified by a labeled anti-immunoglobulin.

A portion of ingested food protein is normally absorbed intact across the gastrointestinal mucosal barrier, permitting the formation of an immune response and low levels of circulating antibody to these food proteins (79,83,84). It has been suggested but not proven that certain allergic reactions may be caused by circulating immune complexes containing food antigens complexed with IgE or IgG antibodies (85,86). Such immune complexes are, however, more likely to be a normal physiologic mechanism for clearing the food antigens from the circulation and not pathogenic (87).

To date, there is no clinical evidence that circulating food immune complexes cause any form of human disease. Patients with IgA deficiency may have abnormally high concentrations of circulating immune complexes to bovine albumin, but the pathophysiologic role of these complexes is unknown (87,88). No support exists for the use of assays for food immune complexes in the diagnosis of allergic disease.

UNCONVENTIONAL TREATMENT METHODS

The three principals of treatment for allergic patients are (1) allergen avoidance, (2) medications to reverse the pathophysiologic abnormalities, and (3) specific allergen immunotherapy. Nonspecific immunomodulation using monoclonal anti-IgE therapy has been shown to be effective in some cases of atopic disease, such as persistent asthma and chronic idiopathic "spontaneous" urticaria (89). Allergy management must also account for the patient's physical, emotional, and social conditions, so the program is ideally individualized for each case. Every form of treatment, including allergen avoidance, is subject to undesired adverse effects. Treatment should be monitored for both efficacy and complications.

This section covers controversial therapies that are ineffective or inappropriate for allergy. These methods are considered in two categories: (1)

treatments that have not been shown to be effective for any disease and (2) treatments that are not appropriate for allergy but may be effective in other diseases. In both of these categories, ineffective treatments are not without risk for adverse effects (90,91), including undertreatment and side effects (92).

Treatment Methods of No Value

This section discusses ineffective treatments for all diseases, including allergy. Although without proven therapeutic benefit, some patients may experience temporary symptomatic improvement or sense of well-being. Such placebo effect accompanies any therapeutic maneuver, whether effective or not.

Neutralization

Neutralization (also called symptom-relieving) therapy (60,93–95) is an extension of provocation–neutralization testing, as discussed earlier. It consists of self-treatment by injection or sublingually with extracts of inhalant allergens, foods, or chemicals at a concentration determined from the prior symptom-neutralizing testing. The goal is to relieve or prevent symptoms on environmental exposure. An ongoing maintenance program is sometimes recommended.

Clinical ecologists who prescribe neutralization therapy for "chemical and food hypersensitivity" frequently combine it with megadose vitamin therapy, mineral or amino acid supplements, and antioxidants. Drug therapy is usually condemned by these practitioners as a form of chemical exposure, although oxygen, mineral salts, and antifungal drugs are frequently prescribed. None of these measures—either singly or in combination—has been evaluated in properly controlled trials to determine efficacy or potential adverse effects.

There is no rational mechanism based on currently accepted immunologic theory to account for immediate symptom neutralization by this method. Published studies are either anecdotal or inadequate, suggesting that any beneficial effect is based on suggestion (68).

Acupuncture and Moxibustion

The ancient Chinese procedure of acupuncture has been used over the centuries to treat virtually every disease. Moxibustion consists of burning dried mugwort at the acupressure sites (acupoints). These are now popular in Western culture as well, although modern medical science offers no theoretical support for its continued use. Variations in technique include acupressure, laser acupuncture, and catgut implantation at acupoints (96). It is employed exclusively by some

practitioners or as an adjunct to pharmacotherapy, herbal therapy, homeopathy, naturopathy, and psychotherapy. A significant number of allergic patients in the United States have tried acupuncture at some time for relief of asthma, allergic rhinitis, and allergic dermatoses. It is also used by patients who have other nonallergic symptoms or medical conditions incorrectly diagnosed as allergic. Although some rhinitis patients report subjective benefit (97), there have been no reported studies documenting either objective improvement or long-term alteration in the course of allergic disease (98–101). The best clinical trials in allergic diseases are of low quality regarding methodology, inconsistency as to the type of patients, interventions, and outcome measures, and they yield contradictory results (102–105). Furthermore, neither acupuncture nor moxibustion is necessarily safe (106,107).

Herbal Therapy

Herbs are plant products, including extracts, employed as treatment for disease. The variety of plants used for this purpose is quite extensive and typically originate from Asian countries. The sources of the plants are often obscure and obviously variable. Herbal therapy is especially popular among those who choose to prescribe or use nontraditional methods in allergy, often in conjunction with acupuncture. Acupoint herbal patching is the local acupuncture stimulation with an herbal patch (108). Weak pharmacologic properties have been shown for a few of them (109,110). Oral ingestion is the usual route of administration, although topical application for skin disease is occasionally prescribed.

A number of randomized controlled clinical trials have been published in adult and childhood asthma (111–114), allergic rhinitis (115,116), and atopic eczema (117–119). Results are mixed with a significant bias in study design because of heterogeneity of herbs, poor quality of blinding, small sample sizes, and inadequate reporting and endpoint measurements. Food Allergy Herbal Formula-2 (a nine-herb mixture) has shown *in vitro* immunomodulatory effects; however, efficacy for improving tolerance to food allergens has not been demonstrated (120).

Homeopathic Remedies

Homeopathy is an alternative form of "healing" based on treating "like with like," that is, the causative agent of a disease is administered in exceedingly small amounts therapeutically. Homeopathic remedies consist of extracts of a number of natural substances, including plants, animal products, and insects. These extracts are diluted in a serial manner through a process known as succussion, which is merely the violent shaking of a container of diluted extract.

Homeopathists also prescribe "natural" hormones in the form of orally administered extracts of animal adrenal cortex, thyroid, thymus, pancreas, and spleen. There is no evidence that homeopathic remedies have any therapeutic benefit for any disease, including allergy (52,121,122).

There is no scientific theory to support homeopathic practice, despite its popularity. Because this procedure has a superficial resemblance to immunotherapy or desensitization, it is not surprising that homeopathic practitioners offer their remedies for the treatment of allergic diseases.

Detoxification

Detoxification for allergy treatment is recommended by those who subscribe to the unfounded theory of allergic toxemia, that is, that an allergic state can be induced by toxic damage to the immune system from exposure to environmental chemicals (76,77). Supporters of this concept believe that immunotoxic lipid-soluble chemicals may be stored in body fat for long periods of time.

The method consists of a program of exercise and sauna. High-dose niacin is given to induce erythema. Body fluids are replenished with water and electrolytes. Certain "essential" oils are prescribed, presumably to help replace fat-soluble chemical contaminants. This procedure takes about 5 hours and is repeated daily for 20 to 30 days.

The theory of immunotoxicity as a cause of allergic disease is unproved and contrary to an extensive body of clinical experience. The concept that augmenting blood circulation, vasodilatation, and oral ingestion of vegetable oils can mobilize "toxins" from fat into sweat is untested. The potential dangers of this program have not been adequately studied.

Injection of Food Extracts

Anaphylaxis and urticaria can, in some instances, result from food ingestion if IgE antibody to the relevant food exists in the patient. Fatal or life-threatening anaphylactic reactions can occur from eating minute quantities of the food, most often in peanut allergy. The only accepted method to prevent food anaphylaxis is avoidance.

Specific allergen immunotherapy to eliminate or reduce the anaphylactic sensitivity in IgE-mediated food allergy is an active area of research currently. However, some practitioners routinely prescribe food extract injections, often because of (1) positive food skin or *in vitro* test results in the absence of clinical allergic reactions to those foods, or (2) nonallergic intolerance to foods without

evidence of specific IgE antibodies. In neither case, there is evidence that immunotherapy with food extracts is clinically beneficial.

Urine Injections

The drinking of urine was an ancient healing practice. The modern medical literature contains a single paper on "urine therapy," published in 1947, in which intramuscular injections of the patient's own urine were recommended for a long list of symptoms and illnesses, including allergy (123). In recent years, a small number of medical and "alternative" practitioners have revived this unconventional procedure, claiming that urine contains unspecified chemicals produced by the patient during an allergic reaction and that injections of these chemicals inhibit or neutralize future allergic reactions. There is no scientific evidence to support autogenous urine injections, nor are there clinical reports that the treatment is effective.

The risk of injecting urine is potentially serious, because soluble renal tubular and glomerular antigens are normally excreted in the urine. Repeated injections of these antigens could theoretically induce autoimmune nephritis.

Enzyme-Potentiated Desensitization

A modification of conventional allergen immunotherapy by mixing β-glucuronidase with an exceedingly low dose of allergen is known as enzyme-potentiated desensitization (EPD) (124). The treatment is based on an unproved theory that β-glucuronidase acts on type 2 helper T cells, thereby regulating immune response.

This is recommended as a single preseasonal intradermal injection for seasonal pollen allergies or every 2 to 6 months for patients with perennial symptoms. For unexplained reasons, practitioners who use this procedure advise the patient to avoid common food allergens, food additives, and all medications for 3 days before and 3 weeks after each injection and to avoid allergen exposure for 1 to 2 days before and after the injection and consume a special "EPD diet." It is recommended for not only atopic and anaphylactic diseases but also for ulcerative colitis, irritable bowel syndrome, rheumatoid arthritis, migraine headaches, Ménière disease, petit mal seizures, chronic fatigue syndrome, "immune dysfunction syndrome," food-induced depression and anxiety, and childhood hyperactivity. One controlled trial of food extract-containing EPD in "hyperkinetic syndrome" of children reported tolerance to the responsible food (125).

Several controlled short-term clinical trials reveal conflicting results on

symptoms of allergic rhinitis or asthma (126–131), but objective measures of disease activity are either absent or were not measured (130). No trial has compared EPD treatment with either the allergen or enzyme alone. There is no information about possible chemical or biologic alteration of the allergen when mixed with the enzyme.

Bioresonance (Biophysical Information Therapy)

Bioresonance therapy is the application of an electronic circuit to measure skin-resistance claimed to diagnose variety of diseases and for treatment by stimulating a change of "bioresonance" in the cells. This unscientific procedure has been used therapeutically in childhood atopic dermatitis, but a double-blind trial showed no effect (73).

Speleotherapy and Halotherapy

Speleotherapy requires that a patient breathe air in a subterranean environment. Halotherapy is the inhalation of micronized dry salt within a chamber that mimics a salt cave environment. These are used primarily in Europe, where it is believed to be therapeutic for patients with asthma and other respiratory diseases. Published trials using methodology of reasonable quality do not establish efficacy for these treatments (132,133).

Inappropriate Treatment Methods

Each of the forms of therapy discussed below have a specific role in the management of certain diseases, but not for treatment of allergy.

Vitamin, Mineral, and Nutrient Supplementation

Dietary supplements have been recommended to relieve symptoms or as a cure for patients with allergies. These include well-recognized compounds, such as vitamins, minerals, amino acids, flavonoids, and proteoglycans, as well as plant or animal extracts, and "medicinal" herbs, of doubtful source and purity (134).

There are various theories to rationalize their use. The usual explanation is a deficiency of some as a cause of allergy. There is no scientific basis for this, nor have there been controlled clinical trials demonstrating that replacement by dietary supplementation is efficacious for any allergic disease. Fortunately, most patients are not harmed by taking supplements, although excessive intake of fat-soluble vitamins could result in toxicity. Evidence for vitamin D deficiency in asthma (135,136) and its therapeutic supplementation efficacy are doubtful (137). Proponents of therapy with antioxidants—such as vitamin C and E and glutathione—justify the practice by citing evidence that allergic inflammation

generates free radicals that cause oxidative damage to tissues (138). Although toxic oxygen metabolites are activated during the course of certain inflammatory reactions, the kinetics and localization of these events and the normal activation of endogenous antioxidants make it unlikely that ingestion of these dietary supplements would be effective.

Diets

Avoidance is the only certain method for managing food allergy, although trials of modified food allergen immunotherapy are currently promising. In most cases, the food allergen is a single item or a single food class, so avoidance can be accomplished without compromising the nutritional status of the patient.

An unsubstantiated concept that numerous subjective symptoms, behavioral problems, and emotional illness are attributed to "multiple food allergies" can result in the unnecessary restriction of large numbers of foods. The risk of nutritional deficiency is obvious, although in practice, many patients abandon highly restrictive diets because of the lack of any long-term benefit.

Proponents of the concept of multiple food allergies sometimes recommend a "rotary diversified diet," in which the patient rotates foods so that the same food is eaten only once every 4 to 5 days (139). To do this, it is necessary to keep extensive and accurate records, causing further unnecessary and time-consuming attention to diet and symptoms (15). This diet is usually favored by those who subscribe to the concept of multiple chemical sensitivities, because multiple food "sensitivities" are believed to also occur in this illness.

Environmental Chemical Avoidance

Allergists recommend a reasonable and cost-effective program of allergen avoidance for patients with respiratory allergy. The usual advice is to reduce house dust and dust mite exposure by using special casings for the bedding and by removing bedroom carpeting. Similar measures can be taken to lessen indoor levels of airborne mold spores and other allergens. Avoiding occupational exposure to proven workplace allergens and irritants, such as animals, isocyanate fumes, acid anhydrides, wood dusts, and grain dusts, are mandatory for patients with documented occupational asthma or hypersensitivity pneumonitis caused by these agents. Proven clinical allergy to foods can be managed by selective food elimination.

In contrast, the concept of multiple food and chemical sensitivities discussed earlier carries with it a recommendation for extensive avoidance of environmental "chemicals." Typically, patients diagnosed by unproved methods

—usually provocation–neutralization—have unexplained multiple chronic vague symptoms. They are advised to avoid any exposure, even minute amounts, of chemicals (12,140,141) such as pesticides, organic solvents, vehicle exhaust fumes, gasoline fumes, household cleaners, glue and adhesives, new carpets, and many others. There is no proof that these drastic measures are helpful; on the contrary, there is evidence for significant psychologic harm (142).

Avoidance of all food additives, environmental synthetic chemicals, and even some natural chemicals is recommended, but the extent of avoidance varies with the enthusiasm of the patient and physician and not on scientific evidence of efficacy. Patients often avoid scented household products, synthetic fabrics and plastics, and pesticides. They generally try to limit exposure to air pollutants, gasoline fumes, and vehicle exhaust fumes. Several isolated rural communities have been established for these patients.

Antifungal Medications

The unsubstantiated theories of "Candida hypersensitivity syndrome" and disease caused by indoor molds, both discussed earlier, have prompted some physicians to recommend a treatment program of antifungal medications and a special "mold-free" diet. Although some antifungal drugs are effective in the treatment of cutaneous and systemic candidiasis, their use in the unsubstantiated "Candida syndrome" cannot be justified. A controlled clinical trial showed that nystatin did not differ from placebo in its effect on such patients (143).

Eradication of *Helicobacter pylori* Infection

Chronic urticaria is a particular vexing problem for allergists. An underlying systemic infection has long been suspected as one of many causes. At least half of the population is infected at some time with *H. pylori*, which may result in peptic ulcers and stomach cancer. Systemic effects of increased mucosal permeability to alimentary antigens, immunomodulation, and autoimmunity have been proffered to explain extra-gastrointestinal disorders, such as chronic urticaria. Reports that eradication of *H. pylori* resulted in disappearance of the urticarial lesions in some patients have led to randomized controlled trials. However, results are mixed, probably because of problems with methodology (144–146).

Immunologic Manipulation

Allergic diseases affect a minority of the population who are exposed to allergens. Allergen avoidance prevents disease but does not alter the underlying immunologically induced hypersensitive state. It is not currently possible to

manipulate the immune system in such a way to remove a patient's specific allergic sensitivities completely and predictably without also inhibiting other necessary immune functions. Specific allergen immunotherapy and monoclonal anti-IgE therapy, both discussed elsewhere in this book, do not achieve this goal, although they are clinically beneficial in most carefully selected cases.

Therapeutic γ globulin administration is a standard treatment for documented IgG antibody deficiency, and they have proved effective for this purpose. γ Globulin infusions have been recommended by some practitioners for allergy, but until effectiveness is shown by proper double-blind studies, such treatment should be considered experimental.

■ UNPROVEN METHODS FOR ALLERGY PREVENTION

Research on allergy prevention has emerged in recent years because of evidence for a population increase in allergic diseases. Various prevention methods have been proposed and are being studied for efficacy and safety. To date, the results are controversial, and none has been established as standard. Some of these are discussed below, recognizing that one or more of these methods may or may not be recommended in the future.

Probiotics

Probiotics are nonpathogenic living microorganisms, usually a component of the normal human gut. They have been administered orally as therapy for allergic diseases, especially in atopic eczema and food allergy. Theoretical considerations include the "hygiene hypothesis" (lack of bacterial antigens in early life inhibiting the T_H2/T_H1 switch) and inadequate development of immune tolerance by intestinal microbiota.

Probiotics are currently popular as prevention for subsequent atopic disease when administered prenatally, during breastfeeding and for infants and children. Both prenatal and postnatal studies are hampered by heterogeneity of microbial strain selection and dosage. Clinical trials have provided mixed results (147–151) and are judged of low quality because of bias, inconsistency, and imprecision results (152). They are safe for short-term use, but potential long-term effects are unknown.

Long-Chain ω-3 Polyunsaturated Fatty Acids

Long-chain ω-3 polyunsaturated fatty acids (LCPUFA) supplementation is based

on the correlation of allergy becoming more prevalent globally over the past 20 years with a decline in consumption of LCPUFA found in fish oil. Additionally, it inhibits inflammation, resulting in a theory that supplemental dietary fatty acids may alter the developing neonatal immune system before allergic responses are established (153). Epidemiologic data are suggestive of an effect on asthma in children but not adults (154). A number of studies on administration during pregnancy or lactation reveal insignificant effect on childhood allergy (155).

Supplemental Folic Acid

Maternal prepregnancy folic acid supplementation prevents fetal malformation, particularly neural tube defects. This treatment has also been suggested as prevention of childhood allergic disease, especially asthma. Publications on studies of varying quality suggest no significant effect (156), although there is a suggestion that supplementation with a high dose of folic acid in pregnancy may increase and a low dose may decrease the risk of infant asthma (157,158).

Breastfeeding

The relationship between breastfeeding and allergic disease prevention is controversial. Research has been hampered by ethical considerations, limitations in study methods, and evaluation of results. Current evidence is inconclusive concerning development of eczema, asthma, allergic rhinitis, and food allergy (159–161).

REMOTE PRACTICE OF ALLERGY

In allergy practice, the proper diagnosis and treatment for each patient is based on a thorough history and physical examination by a physician knowledgeable about allergic diseases. In many cases, testing for specific sensitivities by skin or *in vitro* tests, other laboratory tests, imaging studies, and other diagnostic procedures may be indicated to supplement the findings from the history and physical examination. Accurate diagnoses and appropriate treatments require knowledge of the patient's current and past symptomatology, physical findings, and physiologic and biochemical tests (where indicated). The results of allergy skin tests and *in vitro* tests for IgE antibodies do not distinguish whether the patient has current, present, or future symptomatic disease; therefore, these test results alone reveal only potential—but not necessarily clinical—sensitivities. They cannot be used alone as the basis for recommending drug therapy or allergen immunotherapy.

Skin and *in vitro* testing for IgE antibody sensitivities are readily available. Certain practitioners do in fact diagnose and recommend treatment for allergy solely from these test results. This is known as the remote practice of allergy (162). It is clearly unacceptable, because allergic disease occurs through a complex interplay of constitutional, environmental, and allergic factors, all of which must be known to the treating physician prior to recommending effective management and to avoid unnecessary, inappropriate, and potentially dangerous treatment.

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Personalized Medicine in Allergy-Immunology

PAUL A. GREENBERGER

INTRODUCTION AND TERMINOLOGY

How can we prescribe the "right medicine for the right patient at the right dose at the right time?" (1,2). By stratifying patients according to the anticipated response to treatment, risk of harms, specific needs, and preferences, personalized or stratified medicine is a method for individualized ("tailored") treatment (1,2). The Food and Drug Administration (FDA) has suggested using the term *personalized medicine* more broadly "to all stages of care including prevention, diagnosis, treatment, and followup" (1). The term *precision medicine* implies using a molecular approach for genetic mapping to provide individualized treatments, assess risk of disease, and likelihood of adverse effects of treatment (1,3). The National Academy of Medicine (4) emphasized that *precision medicine* would "make use of genomic, epigenomic, exposure and other data to define individual patterns of disease, potentially leading to better individual treatment."

Stated differently, "precision medicine as treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations" (5).

Pharmacogenomics is "the study of variations of DNA and RNA characteristics as related to drug responses."

For example, how do variations in DNA sequence, gene expression, and copy number correlate with a patient's response to treatment or risk of harms? Or how might environmental exposures alter mRNA so that patients experience reduced responses to medications or greater risk of harms? Physicians and health care professionals learn about the pharmacology or physiologic response to treatments so as to identify patients who are very good or relatively poor responders to treatment. Some classes of medications result in far greater effectiveness in terms of treatment results and lack of harms than others. It has

been reported that about 40% of patients with asthma receive therapy that is ineffective, perhaps because of inadequate or ineffective dosing or lack of patient adherence (6). A classic example of pharmacogenomics is mutations in the G6PD gene, causing deficiency. A variety of drugs, including dapsone and primaquine, can result in hemolytic anemia if administered to a patient with G6PD deficiency. In Chapter 17A, a number of human leukocyte antigen (HLA) variants associated with drug hypersensitivity (e.g., HLA-B*5701 and abacavir) are described, also examples of pharmacogenomics.

From the regulatory (FDA) (1) and likely insurance/payer perspective, *clinical utility* describes "the relevance and usefulness of an intervention in patient care; in other words, how much value does it add?"

In this perspective, value is the benefit/cost and may/may not be calculated in a manner that includes the direct and indirect benefits and costs. In the design of clinical research trials, identifying patients likely to be good responders is called *predictive enrichment,* which "utilizes phenotypes such as demographic characteristics, history, pathophysiology, or genomic information so that there is greater efficiency in a research study of a new treatment."

Heterogeneity of Responses

The basis for such a strategy is the significant heterogeneity of treatment responses. Typically, new treatments may receive regulatory approval when, among many other factors, there are two phase 3 clinical trials that show efficacy (superior to placebo) and acceptable safety. Often, there is an open public meeting of an FDA advisory committee. There must be significance of outcome markers in a large population of patients, but that can also translate into relatively small absolute differences in responses, such as in improvement in forced expiratory volume in 1 second (FEV_1) or reduction in numbers of exacerbations of asthma when expressed on an annual basis. The *relative* change can be large, for example, "there was a fourfold increase in FEV_1 (active treatment 10% versus placebo treatment 2.5%)." The *absolute* difference of 7.5% in FEV_1 may not translate into meaningful improvement in health care outcomes in patients with asthma. And will there be fewer exacerbations requiring oral corticosteroids for 3 days or improved overall quality of life from the new treatment? Furthermore, although the treatment is efficacious and safe, not every patient will experience a 10% increase in FEV_1.

Using data from a randomized, double-blinded, double-dummy, placebo-controlled, parallel group, 12-week, trial of asthma comparing montelukast 10

mg and chlorofluorocarbon-beclomethasone dipropionate 200 µg twice daily, the investigators had two primary endpoints: change in FEV_1 and daytime asthma symptom score (7). The mean improvement in FEV_1 at 12 weeks was 13.1% with beclomethasone dipropionate, compared with 7.4% for montelukast and 0.7% with placebo (7). The average change for daytime symptoms was −0.62 for beclomethasone dipropionate, −0.41 for montelukast, and −0.17 for placebo on a 336-point scale (7). Considering changes in FEV_1, the median (middle patient) improvement with beclomethasone dipropionate was 11%, whereas the mean increased by 13% (7). Because the mean exceeded the median, there had to be at least a few large responders or some extremely large responders, with quite a few poor or modest responders. Not surprisingly, the most frequent improvement in FEV_1 at 12 weeks was from 0% to 10%, but some patients experienced >50% improvement in FEV_1. A few patients had a decline in FEV_1 by >30% (7). The study was designed so that a response to treatment would be defined by at least 6% improvement in FEV_1. From that perspective, there were 22% of patients who didn't exhibit a response in FEV_1 with beclomethasone dipropionate, and 34% who didn't improve at least by 6% with montelukast (7). These data highlight the considerable distribution of changes in FEV_1 with two controller medications as well as identifying patients who didn't respond (by at least 6%). Clearly, one would like to administer beclomethasone dipropionate to the patients who are likely to increase their FEV_1 by 30% to 50% over the next 12 weeks. Similarly, there were some patients whose FEV_1 increased by >30% with montelukast (7). In the inclusion criteria for this trial, the patients had to have at least 15% increase in FEV_1 with albuterol. Thus, we can't draw any conclusions about what would be the results of treatment with either controller medication in patients with asthma with <15% bronchodilator response.

In an 8-week, crossover study in children 6 to 17 years of age with persistent asthma, organized to compare responses to montelukast 5 to 10 mg daily and/or fluticasone propionate 100 µg twice daily, investigators prespecified a clinically meaningful cutoff of a 7.5% increase in FEV_1 (8). The mean increase in FEV_1 was 1.9% with montelukast and 6.8% with fluticasone propionate (8). The distribution of responses was as follows: 17% of children responded to both medications; 23% responded just to fluticasone propionate; 5% responded just to montelukast; and 55% didn't respond to either medication (8). The characteristics of responders to montelukast were shorter duration of asthma (median 4 years) and younger age-median age 9 years (8). The pattern of type 2

(T_H2) asthma was found for responders to fluticasone propionate, including higher total eosinophil count >350/µL, fraction of expired nitric oxide (FeNO) >25 ppb, concentrations of total immunoglobulin E (IgE) >200 kU/L and eosinophil cationic protein >15 µg/L, PC_{20} methacholine <1 mg/mL, and baseline prebronchodilator FEV_1 < 90% and FEV_1/forced vital capacity (FVC) < 80% (8). Responders to montelukast had prebronchodilator FEV_1/FVC <80% and urinary leukotriene E_4 (LTE_4) concentration ≥100 pg/mg creatinine (8). The dual responders were found to have higher urinary LTE_4 concentrations and lower prebronchodilator FEV_1 and FEV_1/FVC compared to the majority of patients not responding to either treatment (8). In this study, inclusion criteria included a 12% increase in FEV_1 with albuterol or maximum PC_{20} for methacholine of 12.5 mg/mL (8). Thus, we are not informed about patients with persistent asthma who don't have such this expected response to albuterol. Nevertheless, this study illustrates that the good responders to an inhaled corticosteroid (ICS) exhibited the type 2 pattern of allergic inflammation, meaning patients who respond to albuterol and have "allergic inflammation rich" asthma are more likely to respond to ICS treatment. Responders to montelukast had higher baseline urinary LTE_4 concentrations but not the type 2 pattern of asthma. The characteristics of good responders or poor responders to ICS are presented in Table 46.1.

To test whether bronchodilator responsiveness could be a predictor of response to ICS, response to albuterol was not an inclusion criterion in a 6-week study of adults 18 to 55 years of age (9). Patients were required to have baseline FEV_1 from 55% to 85% predicted and PC_{20} < 15 mg/mL (9). The intervention was with hydrofloroalkaline-beclomethasone proprionate 160 µg twice daily with a primary endpoint of ≥5% improvement in FEV_1. The mean FEV_1 increased from 2.62 to 2.84 L (8.4%) (9). There was substantial heterogeneity of responses to the ICS in that 39 subjects (54%) were responders to ICS and 33 subjects (46%) were nonresponders (9). In the group of 39 responders, there was remarkable heterogeneity in that 7 of 39 patients experienced increases in FEV_1 from 35% to 60%, and 13 of 39 patients had at least a 20% improvement in FEV_1 (9). These data supported the observation that bronchodilator responsiveness predicted response to the ICS (9). Phenotypes of type 2 asthma surprisingly were not predictors of response to ICS in this study.

TABLE 46.1 CHARACTERISTICS OF RESPONDERS TO INHALED CORTICOSTEROIDS IN ASTHMA

GOOD RESPONDERS

Type 2 (T_H2) allergic inflammation

Higher FeNO

Higher serum periostin

Higher absolute eosinophil counts

Sputum eosinophilia

Elevated total IgE concentration

Increased FeNO

Responder to albuterol (≥12% with albuterol)

Ventilation heterogeneity of small airways

LESS FAVORABLE OR POOR RESPONDERS

Non-type 2 asthma

Obesity

Cigarette smoking

Little bronchodilator response with albuterol

Nonadherent

Ineffective inhalation technique

CHARACTERISTICS OF GOOD/POOR RESPONDERS TO TREATMENT FOR ASTHMA

In a study to determine whether there were differences in responses to an ICS between African Americans and European Americans, no differences were identified (10). There was equally effective improvement with hydrofluoroalkane-beclomethasone dipropionate at 160 μg twice daily for 6 weeks. There were two primary outcome markers: the change in asthma control test (ACT) and improvement in FEV_1 (10). The most predictive marker of improvement was baseline ACT score ≤ 19. The mean extent of improvement of FEV_1 was 11.6% (10).

There is an example of a single-nucleotide polymorphism (SNP) in the gene for histone deacetylase (HDAC) (see Chapter 19) that is associated with reduced responses to oral corticosteroids and ICS (11). HDAC serves to deacetylate histones and repress inflammation. Reduced activity of HDAC allows for unchecked, nuclear factor-κB–based inflammation in asthma. The SNP of HDAC1 (rs1741981) was associated with reduced increases in FEV_1 after treatment with prednisolone 15 mg twice daily for 7 days in adults (12.7% versus 37.4% in control patients) (11). Similarly, the response of FEV_1 was reduced in affected children who were treated with an ICS for 8 weeks (14.1% versus 19.4% in control patients) (11).

There are conflicting data regarding effect of SNPs of the corticotropin-releasing hormone receptor 1 gene (CRHR1) and responses to ICS (12,13). Corticotropin-releasing hormone binds to CRHR1 in the pituitary gland to initiate synthesis of adrenocorticotropic hormone. Furthermore, meaningful genetic variants were not associated with responses to ICS in an intensive study of 2,762 subjects from seven clinical trials (14). Much investigation remains to be carried out to identify relevant genotypes and responses to corticosteroids.

Larger responses to the cysteinyl leukotriene receptor 1 (CysLTR1) antagonist, montelukast, have been reported in children with concentrations of urinary LTE_4 > 100 pg/mg creatinine (8). In an 8-week study, the improvements in FEV_1 were >10% in 16% and from 5% to 10% in 17% of children (8). Otherwise, improvements in FEV_1 were smaller. Some patients have improved

with montelukast administration in terms of fewer symptoms and greater numbers of asthma control days. Similarly, in adults with either mild or moderate persistent asthma, the responders to montelukast 10 mg daily had mean urinary LTE_4 >225 pg/mg creatinine compared with 175 pg/mg creatinine for nonresponders (15). The definition of responder required meeting three conditions: (1) >20% reduction of symptom scores, (2) >20% reduction in β_2-adrenergic agonist doses, and (3) an increase >10% in FEV_1 (15). At the end of 4 weeks, there were 25 of 48 (52%) of patients who were the responders (15). In particular, the change in FEV_1 in responders was from 77% to 89% predicted, whereas in nonresponders, the FEV_1 decreased from 79% at baseline to 76% in 4 weeks (15). In an investigation from two clinical trials with montelukast, where 10% to 13% of patients had increases in FEV_1 from 18% to 25% compared with 8% to 10% in the rest of the patients, there were good responder SNPs (rs91227 and rs912278) identified in the cysteinyl leukotriene receptor 2 gene and SNPs (rs4987105 and rs4986832) in the 5-lipoxygenase (LO)-activating protein (ALOX5) gene (16).

The 5-LO synthesis inhibitor, zileuton, inhibits from 26% to 83% of leukotriene production (17) and leads to bronchodilation in the first 60 minutes of 14.6% compared to 0% with placebo (18). In a separate study where treatment was continued for 12 weeks, zileuton, 1,200 mg twice daily, caused the FEV_1 to increase by 20.8% compared with 12.7% in placebo-treated subjects (19). Depending on the contributions of leukotrienes to the pathobiology of asthma, there will be variations in response to zileuton or CysLTR1 antagonists that can be identified empirically.

Short-acting β_2-adrenergic agonists (SABAs), such as albuterol, have a very wide range of responses (increases in FEV_1 and reduction of or prevention of symptoms), and adverse effects (tremulousness and palpitations) (20). In a dose–response study beginning with albuterol, 100 µg, the maximum extent of bronchodilation varies among patients (20). The wild-type genotype at the β_2-adrenergic receptor is designated as B16 Gly-Gly. Polymorphisms at position 16 (Gly16Arg) have been associated with reduced protection from bronchoconstrictor stimuli and smaller degrees of control of asthma in patients using SABAs and long-acting β agonists (LABAs) (21–24). However, in patients using ICS, this finding hasn't always been confirmed (22,25). The rationale is that being homozygous for the SNP of the 16th amino acid in the β_2-adrenergic receptor (B16 Arg/Arg) instead of wild type (B16 Gly-Gly) would predispose to

less bronchodilation and more exacerbations (24). There has been a concern that the reduced bronchodilation and loss of control of asthma are more likely to occur in African Americans, of whom about 20% have the B16 Arg/Arg mutation (22). However, when an LABA is *added to baseline* ICS therapy, irrespective of genotypes, there have not been large clinical differences between responses of Caucasians and African Americans (25).

Omalizumab has been approved in the United States since 2003 for persistent severe asthma and has multiple biologic effects (26). Clinical improvement can be established after 16 weeks of treatment (27). For example, in a large real-world study in the United Kingdom, the ACT score increased from 10 at baseline to 16 by 16 weeks (27). No further improvement in the ACT score occurred with continued treatment through 8 and 12 months (27). Some characteristics of good responders include (1) experiencing an exacerbation in the run-in period of a clinical trial for patients in steps 2 to 5 persistent asthma, (2) exhibiting type 2 asthma biomarkers, including FeNO >24 ppb, peripheral blood eosinophils >260/µL, and periostin >50 ng/mL, and (3) having more robust *ex vivo* production of interferon (IFN)-α by peripheral blood mononuclear cells (PBMCs) when stimulated with rhinovirus in the presence of omalizumab (the production of IFN-α from PBMCs experimentally is reduced in the presence of IgE cross-linking, but omalizumab interferes with this process) (26,28).

Mepolizumab, the anti-IL-5 monoclonal antibody, was approved in the United States in 2015 for patients aged 12 years and older with severe asthma and an eosinophilic phenotype meaning absolute peripheral blood eosinophils ≥150/µL (currently in the past 4 to 6 weeks) or ≥300/µL in the past year (29,30). There are fewer exacerbations, reduced oral corticosteroids, and increased FEV_1 in responders (29). The reduction in symptoms as measured by the asthma control questionnaire-5 was present as early as 2 weeks (29). Subsequent cluster analysis identified better responders as patients with peripheral blood eosinophils >150/µL combined with a bronchodilator response >16.2% (30). Indeed, when body mass index >30 was incorporated with the first two biomarkers, the response rate was even higher (30).

Endotypes and Phenotypes

Phenotypes are observable characteristics, such as bronchodilator responsiveness, obesity, good/poor adherence, allergic inflammation rich (type 2 asthma), neutrophilic, T_H17-rich inflammation in asthma, poor perceiver, and hypervigilant observer. Alternatively, an endotype is a distinctive subtype of a

disease with its own pathobiology and particular responses to treatment (31). Some proposed examples include aspirin-exacerbated respiratory diseases (formerly Samter syndrome), allergic bronchopulmonary aspergillosis, persistent severe neutrophilic asthma in adults, and asthma predictive index positive children with asthma (31). Identifying such endotypes of asthma could lead to greater predictive enrichment in clinical research trials so as to determine the good or superior responders to a treatment. Alternatively, if the trial of a new therapy for an endotype fails to result in efficacy, then the hypothesis, even if very attractive based on previous investigations, may well be incorrect. Such is the process of scientific investigation. Nevertheless, the path to demonstration of a new treatment's efficacy or lack thereof will have be carried out in a population of research subjects who were more likely to respond. It should be noted that phenotypes can be present in many endotypes (e.g., bronchodilator responsiveness), but an endotype is distinctive as a subtype of the disease (31).

TABLE 46.2 EXAMPLES OF HIGHLY EFFECTIVE INTERVENTIONS AND PERSONALIZED TREATMENTS FOR SELECTED PATIENTS WITH ASTHMA

Avoidance measures for patients with asthma or allergic rhinitis (e.g., animal danders, molds, dust mites)

Establishing shared therapeutic goals with patients so that an action plan can be started by the patient for early treatment of and improved control of exacerbations of asthma

Attempting a step-down approach to medications after 3 mo of effective control of asthma

Recognizing when patients are nonadherent or for other reasons wouldn't meet inclusion criteria for clinical trials, implying that evidence-based approaches may be unsuccessful and that individualized and successful treatment recommendations will not be evidenced based

Utilizing allergen immunotherapy (subcutaneous or sublingual) for patients with asthma and allergic rhinitis

Employing ICS or leukotriene D_4 receptor antagonists in good responder patients

Recognizing limitations of ICS, LABAs, ICS/LABA combinations, long-acting

| muscarinic antagonists, leukotriene D_4 antagonists, 5-lipoxygenase biosynthesis inhibitors, theophylline, and macrolides |
| Identifying good responders to immunobiologics |
| Suspecting cough equivalent asthma in patients and clearing the cough with a short course of prednisone and continued therapy with an ICS |
| Determining how important the unified (integrated) airway is for each patient to optimize management |

ICS, inhaled corticosteroids; LABA, long-acting β agonists.

EXAMPLES OF EFFECTIVE AND PERSONALIZED INTERVENTIONS

Asthma is a complex disease, and many patients are not achieving control even with high-dose ICS/LABA (32), immunobiologics, and oral corticosteroids. Many patients with persistent asthma have allergic rhinitis and gastroesophageal reflux, whether symptomatic or not. Perception of dyspnea may be impaired or in other patients, there is hypervigilance regarding symptoms with no physiologic evidence of airways obstruction or a truncated inspiratory flow loop. Or, vocal cord dysfunction or hyperirritable larynx coexists with persistent or intermittent asthma, thus requiring a high level of clinical acumen. In attempting to institute personalized approaches, it is advisable for the physician or health care professional to reassess their own decision-making focusing on the patient's level of control of asthma in perspective to medications and other interventions and comorbidities. Some examples of what can be very highly effective personalized/individualized treatments for certain patients are presented in Table 46.2.

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